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Full Paper

Mechanosynthesis of *N*-Methyl Imines Using Recyclable Imidazole-Based Acid-Scavenger: In Situ Formed Ionic Liquid as Catalyst and Dehydrating Agent

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1,1′-(1,4-Butanediyl)bis(imidazole) was prepared by a modified method and its application as an efficient promoter was demonstrated for the mechanosynthesis of *N*-methyl imines using ball milling as a non-conventional process under solvent-free conditions. In this new protocol design, the bis-imidazole acted as a recyclable acid-scavenging agent. This efficient approach to the *N*-methyl imines displays a combination of the synthetic virtues of a non-conventional condensation reaction with ecological benefits and convenience of a facile mechanosynthetic process. The current method has advantages such as reduced waste by avoiding solvent, exclusion of hazardous materials during the reaction, elimination of handling an anhydrous gas in an evacuated container or a solution of methylamine in ethanol, good yields for relatively unreactive benzaldehydes containing electron-donating substituents, short reaction times, and metal- and acid-free conditions. Furthermore, the promoter was easily regenerated and reused several times with no significant loss of activity.

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Introduction

Mechanochemistry has been developed as an applicable technique that enables a cleaner and green approach to chemical transformations.[1] The ball milling process was initially used to grind materials into extremely fine powders, since then it has progressed to playing a role in solvent-free organic synthesis to minimize the use of toxic and volatile organic solvents and reduce environmental pollution. In spite of numerous papers that have been published using the ball milling process in a variety of organic syntheses, in comparison with other methods of energy entry such as microwave and ultrasound, little effort has been made in view of organic syntheses using a ball milling technique which utilises mechanical energy (friction, impact, collision).[2] Planetary ball mills have been broadly utilised in laboratories for the synthesis of catalysts,[3] heterocycles,[4] metal complexes,[5] catenanes and rotaxanes,[6] the formation of metal–organic frameworks (MOFs),[7] C–C bond formation reactions, protection of functional groups, fullerenes, and redox processes.[2]

Imines and their derivatives (Schiff bases) as nitrogen-containing compounds represent key building blocks in organic chemistry. They constitute the core of valuable compounds exhibiting a broad and interesting spectrum of biological activities including antioxidant,[8] herbicidal,[9] antibacterial,[10] antifungal and antifertility,[11] antitumour,[12] antitubercular,[13] antiproliferative,[14] analgesic, anti-inflammatory and antipyretic,[15] and anticancer and antifungal.[16] Certain Schiff bases often exhibit noteworthy properties such as aggregation,[17] corrosion inhibition,[18] fluorescence,[19] photoluminescence,[20] and can act as dyes and pigments.[21] They have been studied for the treatment of diseases, such as leishmaniasis, trypanosomiasis, and malaria.[22–25] Schiff-bases play an important role as intermediates in a variety of organic syntheses such as the asymmetric synthesis of α-amino nitriles,[26] preparation of secondary amines,[27] and cycloaddition reactions.[28,29] Schiff-bases have been widely applied as the ligand in metal complexes,[30,31] and some of these complexes displayed biological activity including anti-urease activity.[32] These interesting features encouraged much effort towards the synthesis of *N*-methyl imines and imine derivatives as valuable lead compounds.[33–44] However, some of these methods have drawbacks such as toxic noxious gas handling, long reaction times, moderate yields, use of toxic and volatile organic solvents, use of mineral or Lewis acids, and expensive reagents. Therefore, the development of a simple and clean method for the synthesis of imine derivatives is highly attractive. The basic idea in this paper is to use an imidazole-based promoter as an acid-scavenger reagent to form an in situ imidazolium ionic liquid in the course of the reaction; the formed ionic liquid can act as a dual solvent–catalyst and dehydrating agent.

Results and Discussion

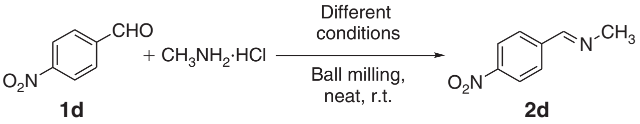
Methylamine is commercially available in three forms: a compressed gas, a methylamine hydrochloride salt, and a 40 % aqueous solution. The 40 % methylamine solution is not explosive, but it is flammable and should be handled with the usual care taken for toxic flammable liquids, especially regarding exposure to open flame or to an ignition source. Initially, to optimize the reaction conditions, the ball milling of a solid mixture of 4-nitrobenzaldehyde (**1d**) and methylamine hydrochloride was chosen as a model reaction (Scheme 1). The equimolar mixture of the model reactants were ground together at room temperature under solvent- and catalyst-free conditions using a planetary ball mill in which the reaction completely failed after 2 h (gas chromatography–mass spectrometry (GC-MS) analysis) (Table 1, entry 1). No notable difference was observed in the yield of *N*-(4-nitro-benzylidene)methylamine (**2d**) when the model reaction was conducted with higher molar ratio of $CH_3NH_2 \cdot HCl$ to **1d** under the same conditions (Table 1, entry 2).

Interestingly, **2d** was obtained in 99 % yield in the presence of 1,1′-(l,4-butanediyl)bis(imidazolium) (1,4-$(Im)_2Bu$) as a promoter after 30 min (Table 1, entry 4). The reaction of an equimolar mixture of $CH_3NH_2 \cdot HCl$ and 4-nitrobenzaldehyde afforded **2d** in 98 % yield within 10 min (Table 1, entry 6); however, a shorter milling time of ~5 min led to a reduction in the yield (Table 1, entry 7). Decreasing the amount of promoter caused a gradual decline in the yield (Table 1, entry 8) while no difference in the yield of **2d** was observed with increasing promoter loading within 5 and 10 min (Table 1, entries 9 and 10).

The influence of technical parameters such as revolutions per minute (rpm), and size and number of balls in the mill on performing the model reaction were investigated. As shown in Table 2, the results displayed that rpm have an important influence on the yield of the desired product, at which point the best yield of **2d** was observed at 600 rpm of the planetary ball mill within 10 min (Table 2, entries 1–3). As reported in the literature,[45] the parameters such as size and the number of milling balls directly influence the active surface area and total mass of the milling balls. While the other parameters were kept constant, the size and the number of milling balls were changed. When experiments were carried out with a larger size and higher number of mill balls, **2d** was afforded in higher yield (Table 2, entries 4 and 5).

To investigate the scope as well as the effectiveness of the non-conventional protocol for the synthesis of the *N*-methyl imines, a variety of aryl and heteroaryl aldehydes were screened under the optimized reaction conditions (Scheme 2).

The results indicated that the electronic properties and the steric demand of the substituent on the aryl aldehyde play a decisive role on the yield of the desired product (Table 3). The aryl aldehydes bearing electron-withdrawing substituents gave higher yields than those with electron-donating substituents as it was expected (Table 3, entries 2, 4, 8, 10, 13, and 15). It is



Scheme 1. Optimization of the reaction conditions.

Table 1. Effects of 1,4-$(Im)_2Bu$ loading, reactants molar ratio, and the milling time on the reaction of 4-nitrobenzaldehyde (1d) and methylamine hydrochloride

Reaction conditions: number of ball mill: 4, rotation speed: 600 rpm, ball mill diameter: 7 mm, room temperature, solvent free. Entry in bold shows optimized reaction conditions

Entry	Amount of promoter [g]	Aldehyde:$CH_3NH_2 \cdot HCl$ [mmol/mmol]	Time [min]	Yield[A] [%]
1	—	5/5	120	0
2	—	5/10	120	0
3	0.5	5/10	120	99
4	0.5	5/10	30	99
5	0.5	5/5	30	98
6	**0.5**	**5/5**	**10**	**98**
7	0.5	5/5	5	76
8	0.4	5/5	10	78
9	0.6	5/5	5	76
10	0.6	5/5	10	98

[A] Determined by GC-MS.

Table 2. Effects of revolution per minute (rpm) and size and number of mill balls on the reaction of 4-nitrobenzaldehyde (1d) and methylamine hydrochloride

Reaction conditions: amount of promoter/$CH_3NH_2 \cdot HCl$/4-nitrobenzaldehyde (2.6 mmol : 5.0 mmol : 5.0 mmol), milling time (10 min), room temperature, solvent-free

Entry	Number of mill balls	Rotational speed [rpm]	Mill ball diameter [mm]	Yield [%][A]
1	4	600	7	98
2	4	500	7	88
3	4	300	7	52
4	4	600	5	68
5	2	600	7	66

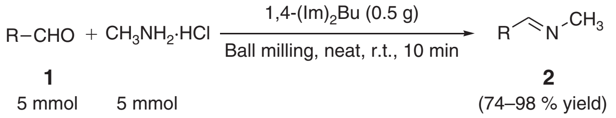
[A] Determined by GC-MS.

noteworthy that 2-methoxybenzaldehyde (Table 3, entry 11) gave the desired *N*-methyl imines in higher yield compared with 3- and 4-methoxybenzaldehyde (Table 3, entries 5, 16) which can be assigned to the decrease of conjugation between the 2-methoxy group and the phenyl ring caused by steric interference in the 2-methoxybenzaldehyde. Furthermore, the heteroaromatic aldehydes (Table 3, entries 19–21) were efficiently converted into the desired *N*-methyl imines in good to excellent yields. Terephthalaldehyde was also transformed into an imine using two equivalents of $CH_3NH_2{\cdot}HCl$ under optimized reaction conditions (Table 3, entry 22).

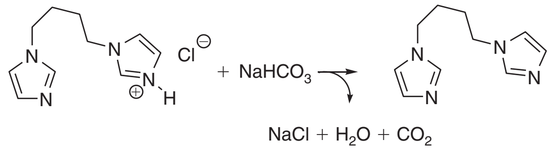
Although the reported methods provide the desired *N*-methyl imines, they suffer from some challenges including the hazardous and specific handling of an anhydrous gas in an evacuated container, unwanted toxicity from residual metal contamination, and non-recyclability of reagent. For example, it was reported that *N*-(4-methoxybenzylidene)methylamine (**2e**) was afforded in 65 % yield by grinding 4-methoxybenzaldehyde, $CH_3NH_2{\cdot}HCl$, and $NaHCO_3$ in a molar ratio of 1 : 5 : 5 for 3 h.[42] In the current method, **2e** was obtained in 80 % yield after 10 min under optimized reaction conditions (Table 3, entry 5). The synthesis of *N*-(*p*-dimethylaminobenzylidene)methylamine (**2g**) failed in the presence of an alkali metal-containing catalyst at room temperature after 2 h or overnight,[42] whereas, it was reported that **2g** was obtained in quantitative yield by the solid-state reaction of the crystalline 4-(dimethylamino)benzaldehyde with gaseous methylamine at room temperature overnight.[33] In addition, the grinding of salicylaldehyde with $CH_3NH_2{\cdot}HCl$ and $NaHCO_3$ in a molar ratio of 1 : 5 : 5 afforded 2-[(*E*)-(methylimino)methyl]phenol (**2h**) in 55 % yield after 1 h in the presence of a non-recyclable alkali metal catalyst.[42] In comparison to the aforementioned methods,[33,42] the present method gave **2g** and **2h** in 80 and 88 % yield under optimized conditions(Table 3, entries 7 and 8). The present protocol exhibited other advantages including avoiding solvent and metal or transition metal catalyst, the regeneration and recyclability of the promoter, a broad-substrate scope, short reaction time, and good to excellent yields.

Recycling of reagents plays a crucial role in large scale and industrial processes; therefore, 1,4-$(Im)_2Bu$ was regenerated by neutralization via the incremental addition of $NaHCO_3$ as the cheapest chemical commercially available (Scheme 3). The regenerated 1,4-$(Im)_2Bu$ was then used in four consecutive runs that afforded **2d** in 98–96 % yield (Table 3, entry 4).

Furthermore, the model reaction was conducted on a 10 g scale to afford **2d** in 82 % yield after 20 min milling time under optimized reaction conditions.



Scheme 2. The synthesis of *N*-methyl imines under optimized reaction conditions.



Scheme 3. Regeneration of 1,4-$(Im)_2Bu$.

Table 3. The reaction of aryl aldehydes with methylamine hydrochloride in the presence of 1,4-$(Im)_2Bu$

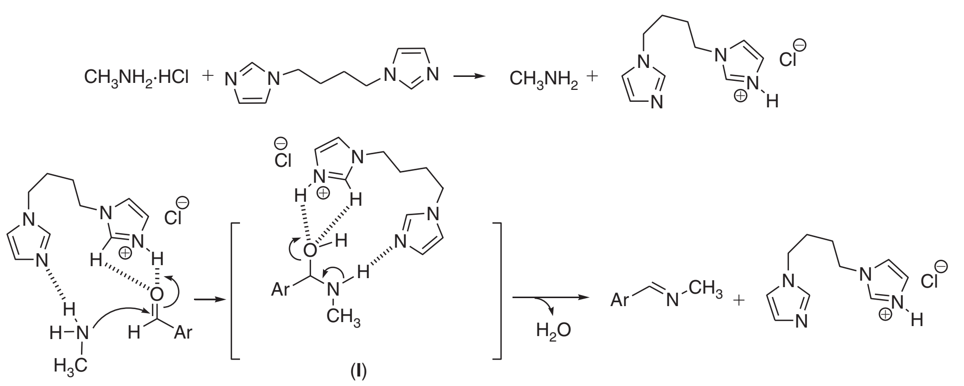
Reaction conditions: aryl aldehyde (5.0 mmol), $CH_3NH_2{\cdot}HCl$ (5.0 mmol), 1,4-$(Im)_2Bu$ (0.5 g), milling time (10 min), room temperature, solvent free

Entry	Aldehyde	*N*-methyl imine	Yield [%][A]	Mp [°C]	
				Found	Reported
1	C_6H_5-CHO	**2a**	94	oil	oil[43]
2	4-Cl$^-$$C_6H_4$-CHO	**2b**	96	oil	oil[43]
3	4-CH_3-C_6H_4-CHO	**2c**	94	oil	oil[43]
4	4-O_2N-C_6H_4-CHO	**2d**	98 (98, 96, 96)[B]	104–106	104–106[43]
5	4-CH_3O-C_6H_4-CHO	**2e**	80	oil	oil[43]
6	4-HO-C_6H_4-CHO	**2f**	91	177–179	175[33]
7	4-$(CH_3)_2N$-C_6H_4-CHO	**2g**	80	54–56	54–56[43]
8	2-Cl$^-$$C_6H_4$-CHO	**2h**	88	oil	oil[43]
9	2-CH_3-C_6H_4-CHO	**2i**	83	oil	oil[43]
10	2-O_2N-C_6H_4-CHO	**2j**	97	oil	oil[42]
11	2-CH_3O-C_6H_4-CHO	**2k**	87	oil	oil[43]
12	3,4-$(CH_3O)_2$-C_6H_3-CHO	**2l**	86	oil	oil[43]
13	3-Cl$^-$$C_6H_4$-CHO	**2m**	90	oil	oil[42]
14	3-CH_3-C_6H_4-CHO	**2n**	85	oil	oil[42]
15	3-O_2N-C_6H_4-CHO	**2o**	94	oil	oil[42]
16	3-CH_3O-C_6H_4-CHO	**2p**	81	oil	oil[42]
17	Salicylaldehyde	**2q**	84	oil	oil[46]
18	Vanillin	**2r**	91	oil	oil[43]
19	Pyridine-4-carbaldehyde	**2s**	92	oil	oil[43]
20	Furan-2-carboxaldehyde	**2t**	82	oil	oil[43]
21	Pyrrole-2-carboxaldehyde	**2u**	74	oil	–
22	Terephthalaldehyde	**2v**	90[C]	88–90	–

[A] Isolated yields.

[B] Product yield after three consecutive recycling in the presence of the recovered solid base catalyst.

[C] Reaction conditions: terephthalaldehyde (5.0 mmol), CH_3NH_2.HCl (10.0 mmol), 1,4-$(Im)_2Bu$ (1.0 g), milling time (10 min), room temperature, solvent-free.



Scheme 4. A plausible mechanism to promote the synthesis of *N*-methyl imines in the presence of 1,4-(Im)$_2$Bu.

Based on the in situ formation of an imidazolium-based ionic liquid and the potential dual solvent–catalyst and dehydrating properties of ionic liquids, a possible mechanism is given for the mechanosynthesis of *N*-methyl imines (Scheme 4). Based on the BASIL process in which the BASF company used *N*-methylimidazole as a base to neutralize a formed hydrogen chloride,[47] in the first step, 1,4-(Im)$_2$Bu can act as acid-scavenger and facilitate the gradual liberation of methylamine, meanwhile, 1,1′-(l,4-butanediyl)bis(imidazolium) chloride (1,4-(Im)$_2$Bu·HCl) generated in situ can be capable of acting as a Brönsted acid catalyst for the synthesis of *N*-methyl imines. It is postulated that 1,4-(Im)$_2$Bu·HCl can activate the carbonyl group by an acidic hydrogen along with the C2–H hydrogen bond of the imidazole ring, and made it more susceptible to attack by the liberated methylamine. The methylamine could also be activated through a hydrogen bond between the nitrogen atom of the imidazole ring and –NH$_2$. Dehydration of the intermediate (**I**) could be promoted in the presence of 1,4-(Im)$_2$Bu·HCl as an efficient dehydrating agent[48–50] and finally *N*-methyl imine is produced. Further investigations aimed at fully elucidating the precise mechanism of this reaction along with the separation and characterization of the intermediates in the course of reaction, are currently underway in our laboratory.

The research on green chemistry development is growing and continually being improved. In order to assess the 'greenness' of a process, scientists must consider and choose the right green chemistry metrics and measure them at key synthesis steps. The right metrics can serve as indicators of reduced manufacturing costs, reflecting lower process materials inputs and outputs, reduced costs from hazardous and toxic waste disposal, improved manufacturing capacity utilisation, and reduced energy demand.[51,52] The common metrics were grouped into three categories: materials efficiency, energy efficiency, and toxicity.[53] In order to assess the greenness of the present methodology, the common materials efficiency metrics were measured and calculated for the synthesis of **2d** (Table 4).

The E-factor was calculated including and excluding CO$_2$ and water as waste in the regeneration of the 1,4-(Im)$_2$Bu (Table 4). An E-factor closer to zero means the process will generate less waste and thus it is more sustainable and greener. However, the E-factor as a metric of the environmental impact of the synthesis process did not consider the hazards and the environmental risk of the produced waste. In general, the reaction mass efficiency (RME) and mass productivity (MP) were the most valuable metrics for driving the adoption of greener processes.[53,54] The present methodology exhibited high atom economy (AE) and RME as well as a good MP.

Table 4. Atom economy (AE^{A}), reaction mass efficiency (RME^{B}), mass productivity (MP^{C}), and environmental impact factor (E-factor^{D}) calculations for the current base-catalyzed mechanosynthesis of 2d

Compound	MW [g mol^{-1}]	Moles [mmol]	Weight [g]
4-NO$_2$-C$_6$H$_4$-CHO	151.12	5	0.76
CH$_3$NH$_2$·HCl	67.52	5	0.34
1,4-(Im)$_2$Bu	190.24	2.6	0.5
4-NO$_2$-C$_6$H$_4$-CH=NCH$_3$	164.16	4.9	0.8
1,4-(Im)$_2$Bu·HCl	227.71	2.6	0.59
NaCl	58.44	2.6	0.15
CO$_2$	44.01	2.6	0.11
Water	18	2.6	0.05

[A] Atom economy $(\%) = \frac{164.16}{(151.12+67.52)} \times 100 = 75.1\%$

[B] Reaction Mass efficiency $(\%) = \frac{0.8}{(0.76+0.34)} \times 100 = 72.7\%$

[C] Mass productivity $(\%) = \frac{0.8}{(0.76+0.34+0.50)} \times 100 = 50.0\%$

[D] E-factor (excluding CO$_2$ and H$_2$O) $= \frac{0.15}{0.80} = 0.19$;

E-factor (inluding CO$_2$ and water) $= \frac{0.31}{0.80} = 0.39$

The energy efficiency is also an important category in green chemistry. The present methodology operates at room temperature and atmospheric pressure under the ball milling process and requires and consumes much less energy compared to high pressure and conventional thermal processing.

The chemical toxicity resources such as PubChem[55] and the EPA's ACToR[56] exhibited no data for the potential toxicity of 1,4-(Im)$_2$Bu. Furthermore, methylamine hydrochloride as a stable solid is safer than as gas or an aqueous solution (40 %) of the methylamine, which are an explosive and extremely flammable gas and a highly flammable liquid, respectively.

Conclusion

In summary, a simple and efficient method for the preparation of *N*-methyl imines in the presence of 1,1′-(l,4-butanediyl)bis (imidazole) (1,4-(Im)$_2$Bu) as a recyclable promoter has been developed. 1,4-(Im)$_2$Bu acts as a multi-task promoter, i.e. as an acid scavenger, in situ Brönsted acid, and dehydrating agent in the synthesis of *N*-methyl imines. The present protocol has advantages such as use of commercially available and safe to handle CH$_3$NH$_2$·HCl, minimal waste and solvent usage, the prevention of handling an anhydrous and toxic gas in an evacuated container, good yields for relatively unreactive benzaldehydes containing electron-donating substituents, shorter reaction time, and metal- and acid-free reaction conditions. In addition, the promoter can be easily regenerated and reused several times with no significant loss of its activity.

Supplementary Material

The modified method of the synthesis of 1,1′-(1,4-butanediyl) bis(imidazole) [1,4-(Im)$_2$Bu], general procedure for *N*-methyl imine formation, regeneration of 1,4-(Im)$_2$Bu, and ^{1}HNMR and ^{13}C NMR copies of 2u and 2v spectral data are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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References

[1] J. L. Do, T. Friščič, *ACS Cent. Sci.* **2017**, *3*, 13. doi:10.1021/ACSCENTSCI.6B00277

[2] A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317. doi:10.1039/C0CS00195C

[3] B. Kubias, M. J. G. Fait, R. Schlogl, in *Handbook of Heterogeneous Catalysis*, 2nd edn (Eds G. Ertl, H. Knozinger, F. Schuth, J. Weitkamp) **2008**, pp. 571–583 (Wiley-VCH: Weinheim).

[4] M. O. M'hamed, *Synth. Commun.* **2015**, *45*, 2511. doi:10.1080/00397911.2015.1058396

[5] A. L. Garay, A. Pichon, S. L. James, *Chem. Soc. Rev.* **2007**, *36*, 846. doi:10.1039/B600363J

[6] C. C. Hsu, N. C. Chen, C. C. Lai, Y. H. Liu, S. M. Peng, S. H. Chiu, *Angew. Chem. Int. Ed.* **2008**, *47*, 7475. doi:10.1002/ANIE.200803056

[7] M. Wilke, M. Klimakow, K. Rademann, F. Emmerling, *CrystEngComm* **2016**, *18*, 1096. doi:10.1039/C5CE01868D

[8] S. Zangade, A. Shinde, S. Chavan, Y. Vibhute, *Orbital: Electron. J. Chem.* **2015**, *7*, 208.

[9] Y. Li, Z. Y. Yang, J. C. Wu, *Eur. J. Med. Chem.* **2010**, *45*, 5692. doi:10.1016/J.EJMECH.2010.09.025

[10] A. Shinde, S. Zangade, S. Chavan, Y. Vibhute, *Org. Commun.* **2014**, *7*, 60.

[11] M. M. Omar, G. G. Mohamed, A. M. M. Hindy, *J. Therm. Anal. Calorim.* **2006**, *86*, 315. doi:10.1007/S10973-006-7095-3

[12] G. Hu, G. Wang, N. Duan, X. Wen, T. Cao, S. Xie, W. Huang, *Yao Xue Xue Bao* **2012**, *2*, 312.

[13] T. Aboul-Fadl, F. A. S. Bin-Jubair, O. Aboul-Wafa, *Eur. J. Med. Chem.* **2010**, *45*, 4578. doi:10.1016/J.EJMECH.2010.07.020

[14] M. Hranjec, K. Starčević, S. K. Pavelić, P. Lučin, K. Pavelić, G. K. Zamola, *Eur. J. Med. Chem.* **2011**, *46*, 2274. doi:10.1016/J.EJMECH.2011.03.008

[15] S. K. Sridhar, A. J. Ramesh, *Biol. Pharm. Bull.* **2001**, *24*, 1149. doi:10.1248/BPB.24.1149

[16] B. S. Creaven, B. Duff, D. A. Egan, K. Kavanagh, G. Rosair, V. R. Thangella, M. Walsh, *Inorg. Chim. Acta* **2010**, *363*, 4048. doi:10.1016/J.ICA.2010.08.009

[17] G. Consiglio, S. Failla, P. Finocchiaro, I. P. Oliveri, S. D. Bella, *Dalton Trans.* **2012**, *41*, 387. doi:10.1039/C1DT11295C

[18] H. Ashassi-Sorkhabi, B. Shabani, B. Aligholipour, D. Seifzadeh, *Appl. Surf. Sci.* **2006**, *252*, 4039. doi:10.1016/J.APSUSC.2005.02.148

[19] N. V. S. Rao, T. D. Choudhury, R. Deb, M. K. Paul, T. R. Rao, T. Francis, I. I. Smalyukh, *Liq. Cryst.* **2010**, *37*, 1393. doi:10.1080/02678292.2010.517328

[20] M. Tümer, S. A. Güngör, A. R. Çiftaslan, *J. Lumin.* **2016**, *170*, 108. doi:10.1016/J.JLUMIN.2015.09.010

[21] P. Krishnamoorthy, B. Ferreira, C. S. B. Gomes, D. Vila-Viçosa, A. Charas, J. Morgado, M. J. Calhorda, A. L. Maçanita, P. T. Gomes, *Dyes Pigm.* **2017**, *140*, 520. doi:10.1016/J.DYEPIG.2016.11.017

[22] V. V. Kouznetsov, A. Gómez-Barrio, *Eur. J. Med. Chem.* **2009**, *44*, 3091. doi:10.1016/J.EJMECH.2009.02.024

[23] H. Cerecetto, M. Gonzalez, *Curr. Top. Med. Chem.* **2002**, *2*, 1187. doi:10.2174/1568026023393066

[24] A. Chipeleme, J. Gut, P. J. Rosenthal, K. Chibale, *Bioorg. Med. Chem.* **2007**, *15*, 273. doi:10.1016/J.BMC.2006.09.055

[25] S. Gemma, G. Kukreja, C. Fattorusso, M. Persico, M. Romano, M. Altarelli, L. Savini, G. Campiani, E. Fattorusso, N. Basilico, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5384. doi:10.1016/J.BMCL.2006.07.060

[26] Z. Jiao, X. Feng, B. Liu, F. Chen, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2003**, 3818. doi:10.1002/EJOC.200300319

[27] Y. Q. Cao, Z. Dai, B. H. Chen, R. Liu, *J. Chem. Technol. Biotechnol.* **2005**, *80*, 834. doi:10.1002/JCTB.1297

[28] M. M. A. R. Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4732. doi:10.1021/OL102062T

[29] L. Filak, T. A. Rokob, G. A. Vaskó, O. Egyed, Á. Gömöry, Z. Riedl, G. Hajós, *J. Org. Chem.* **2008**, *73*, 3900. doi:10.1021/JO800483A

[30] A. Pailleret, F. Bedioui, in *N4-Macrocyclic Metal Complexes* (Eds J. H. Zagal, F. Bediou, J. P. Dodelet) **2006**, pp. 363–438 (Springer Science: New York, NY).

[31] R. Ganguly, B. Sreenivasulu, J. J. Vittal, *Coord. Chem. Rev.* **2008**, *252*, 1027. doi:10.1016/J.CCR.2008.01.005

[32] Â. de Fátima, C. P. Pereira, C. R. S. D. G. Olímpio, B. G. F. Oliveira, L. L. Franco, P. H. C. Silva, *J. Adv. Res.* **2018**, *13*, 113. doi:10.1016/J.JARE.2018.03.007

[33] G. Kaupp, J. Schmeyers, J. Boy, *Tetrahedron* **2000**, *56*, 6899. doi:10.1016/S0040-4020(00)00511-1

[34] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, *Eur. J. Org. Chem.* **2002**, 1184. doi:10.1002/1099-0690(200204)2002:7<1184::AID-EJOC1184>3.0.CO;2-2

[35] A. K. Chakraborti, S. Bhagat, S. Rudrawar, *Tetrahedron Lett.* **2004**, *45*, 7641. doi:10.1016/J.TETLET.2004.08.097

[36] M. Á. Vázquez, M. Landa, L. Reyes, R. Miranda, J. Tamariz, F. Delgado, *Synth. Commun.* **2004**, *34*, 2705. doi:10.1081/SCC-200026190

[37] L. Paquin, J. Hamelin, F. Texier-Boullet, *Synthesis* **2006**, 1652.

[38] M. Gopalakrishnan, P. Sureshkumar, V. Kanagarajan, J. Thanusu, *Res. Chem. Intermed.* **2007**, *33*, 541. doi:10.1163/156856707782565822

[39] K. P. Guzen, A. S. Guarezemini, A. T. G. Órfão, R. Cella, C. M. P. Pereira, H. A. Stefani, *Tetrahedron Lett.* **2007**, *48*, 1845. doi:10.1016/J.TETLET.2007.01.014

[40] H. Naeimi, H. Sharghi, F. Salimi, K. Rabiei, *Heteroatom Chem.* **2008**, *19*, 43. doi:10.1002/HC.20383

[41] E. Ali, M. R. Naimi-Jamal, M. G. Dekamin, *Sci. Iran.* **2013**, *20*, 592.

[42] N. S. Radulović, A. B. Miltojević, R. D. Vukićević, *C. R. Chim.* **2013**, *16*, 257. doi:10.1016/J.CRCI.2013.01.010

[43] N. G. Khaligh, H. S. Abbo, S. J. J. Titinchi, *Res. Chem. Intermed.* **2017**, *43*, 901. doi:10.1007/S11164-016-2672-Y

[44] L. Piazzi, F. Belluti, A. Bisi, S. Gobbi, S. Rizzo, M. Bartolini, V. Andrisano, M. Recanatini, A. Rampa, *Bioorg. Med. Chem.* **2007**, *15*, 575. doi:10.1016/J.BMC.2006.09.026

[45] F. Schneider, A. Stolle, B. Ondruschka, H. Hopf, *Org. Process Res. Dev.* **2009**, *13*, 44. doi:10.1021/OP800148Y

[46] P. A. Nikitina, A. S. Peregudov, T. Y. Koldaeva, L. G. Kuz'mina, E. I. Adiulin, I. I. Tkach, V. P. Perevalov, *Tetrahedron* **2015**, *71*, 5217. doi:10.1016/J.TET.2015.06.032

[47] P. Böhling, *Kem. - Kemi* **2006**, *9*, 10.

[48] A. C. Flores, E. A. Flores, E. Hernández, L. V. Castro, A. García, F. Alvarez, F. S. Vázquez, *J. Mol. Liq.* **2014**, *196*, 249. doi:10.1016/J.MOLLIQ.2014.03.044

[49] M. Krannich, F. Heym, A. Jess, *J. Chem. Eng. Data* **2016**, *61*, 1162. doi:10.1021/ACS.JCED.5B00806

[50] N. G. Khaligh, T. Mihankhah, M. R. Johan, J. J. Ching, *J. Mol. Liq.* **2018**, *259*, 260. doi:10.1016/J.MOLLIQ.2018.03.044

[51] F. Roschangar, R. A. Sheldon, C. H. Senanayake, *Green Chem.* **2015**, *17*, 752. doi:10.1039/C4GC01563K

[52] R. C. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark, *Green Chem.* **2015**, *17*, 3111. doi:10.1039/C5GC00340G

[53] M. J. Mulvihill, E. S. Beach, J. B. Zimmerman, P. T. Anastas, *Annu. Rev. Environ. Resour.* **2011**, *36*, 271. doi:10.1146/ANNUREV-ENVIRON-032009-095500

[54] D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521. doi:10.1039/B206169B

[55] National Institutes of Health (NIH), U.S. National Library of Medicine, National Center for Biotechnology Information, PubChem CID: 5251826. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/5251826 (accessed 13 November 2018).

[56] US Environmetal Protection Agency (EPA), Aggregated Computational Toxicology Online Resource (ACToR). Available at: https://actor.epa.gov/actor/searchidentifier.xhtml (accessed 13 November 2018).