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DES as solvent and catalyst: One-pot synthesis of 1,3-dinitropropanes via Henry reaction with microwave irradiation

Greta Colombo Dugoni,[a] Alessandro Sacchetti [a]* and Andrea Mele[a,b]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Henry reaction was performed by microwave using DES reline (choline chloride / urea), as catalyst and solvent media of the reaction. The optimisation of the condition (temperature, heating mode, time, DESs) allowed, starting from different aromatic aldehyde, to obtain in one-step 1,3 di-nitropropane derivatives, versatile building block, in high yields and~~s in one step~~ under mild reaction conditions.

Introduction

In organic synthesis, reactions leading to the formation of carbon–carbon bond are considered as the cornerstone of building complex molecules. A large class of such C-C bond formation reactions are the results of the coupling between carbanions and electrophiles. Among the carbanions, nitro derivatives have the advantage of an easier preparation and their preparation is less demanding compared to other classes of carbanions. In turn, nitroalkanes[1] appeared to be ideal synthetic building blocks due to their efficient and versatile reactivity profile. The Henry reaction,[2] also known as nitroaldol reaction, is a powerful C–C bond formation reaction leading to nitro-derivatives. The reaction consists of the coupling of a nucleophilic nitroalkane with an electrophilic aldehyde or ketone to produce β-nitro alcohol (Scheme 1), a valuable synthetic intermediate of polyaminoalcohols, polyhydroxylated amines and natural products.[3] The reaction usually occurs under basic catalysis by using the most popular bases, such as carbonates, alkali metal hydroxides, alkoxides, or organic nitrogen bases. The asymmetric Henry reaction has been also thoroughly investigated and many systems based on metal catalysis,[4] organocatalysis[5] and biocatalysis[6] have been proposed. Many studies about the Henry reaction and the synthesis of nitro derivatives in an eco-friendly way have recently been reported, in line with the consolidated trend of the chemical industry to adopt sustainable synthesis, using heterogeneous catalysis,[7] green and non-toxic solvents,[8] microwave irradiation[9] and to seek new efficient technologies with lower energy demand and environmentally friendly processes.[10]

There are two important issues related to the Henry reaction that should be considered: i) the first is related to selectivity. The Henry reaction may in some cases lead to three different products: the β-nitro alcohol **1a**, the dehydration product **1b** and the 1,3-dinitropropane **1c** (see Scheme 1). These latter compounds are useful as important building block for many applications and their synthesis is challenging. ii) As mentioned above, the Henry reaction often requires metal catalysis, thus introducing in the synthetic cycle elements of potential environmental impact.

In this paper, we report our studies on how to overcome both points by using a sustainable approach based on a one-step synthesis mediated by microwaves irradiation and some selected deep eutectic solvents (DESs) as reaction media. Interestingly, the employed DES went beyond the role of solvent, showing a catalytic effect too. Unexpectedly, the reaction conditions here described lead to the serendipitous finding of a highly selective, mild and efficient synthetic route to challenging 1,3-dinitroderivatives (*vide infra*).

In recent years, deep eutectic solvents (DESs) have been proposed as a new class of environmentally green solvent and extensively tested as reaction media.[11]

The concept of DES was first proposed by Abbott in 2003[12] as a mixture of Lewis and Brönsted acids and bases –which can contain a variety of anionic and cationic species – leading to a melting point depression at the eutectic point larger than that calculated assuming ideal mixing.[13]

Compared with conventional organic solvents, DESs, have a low melting point, low volatility, and thus are non-flammable. In addition, DESs can be designed to be biodegradable, non-toxic, inexpensive, and with simple preparation generally requiring no purification steps. These properties promoted DESs as candidates for reaction media in synthesis,[14] electrochemistry,[15] nanomaterials fabrication,[16] biochemistry,[17] separation,[18] and chemical analysis.[19] The most popular DESs are obtained by mixing ammonium or phosphonium salt as hydrogen bond acceptors (HBA), with a variety of hydrogen-bond donors (HBD). The most common in

[a] *Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano, via Mancinelli 7, 20131 Milano, Italy.*
[b] *CNR-ICRM Istituto di Chimica del Riconoscimento Molecolare, "U.O.S. Milano Politecnico", Via L. Mancinelli, 7, 20131 Milano, Italy.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

literature is a combination of choline chloride, a biodegradable and non-toxic ammonium salt, and urea. This DES is sometimes referred to as reline. The easy sample preparation allowed to have a large library of DESs with the possibility of modulation of the physical and chemical properties by selecting the two components, HBD and HBA.

Stimulated by the above reported positive features of DES, and during the study of the Henry reaction in DES, we envisaged that an appropriate composition of the DES could turn it into both a solvent and catalyst. In a first report, Henry reaction has been investigated by Singh with the use of catalytic amounts of reline in methanol as the solvent.[20] When 20% of reline was employed, the expected nitroaldol adduct was obtained in good yields with different aromatic aldehydes. Later, Xuemei[21] reported the enzyme-catalyzed Henry reaction realized using DES as co-catalyst. The lipase from Aspergillus niger (lipase AS) showed excellent catalytic activity toward aromatic aldehydes in water in presence of 30% DES choline chloride:glycerol (molar ratio of 1:2). In both these previous papers, DES was only introduced in catalytic amount, and a molecular solvent was used as reaction medium. Starting from these findings, we studied the Henry reaction in pure DES without the use of other solvents, thus merging catalytic and solvent role. The reaction between 4-fluorobenzaldehyde and nitromethane in pure reline (Ffigure 1) is here reported as a model reaction. Reline could also act as an efficient catalyst for this reaction for the presence of urea in the formulation of this DES. In fact, it is known from the literature that urea derivatives can efficiently promote the Henry reaction through the activation of nitromethane.[22] Further examples of reaction conditions described in this work include: i) the use of different temperatures, ii) the presence of triethylamine (TEA), iii) the use of substituted aldehydes, iv) tests on selected ketones, v) tests on ChCl based DES with different HBD vi) tests on choline acetate-based DES.

Results and discussion

In this study, reline was prepared according to the procedures reported in the literature. Briefly, the preparation involved the combination of choline chloride or choline acetate (HBA) with the different HBDs, urea or glycolic acid at 80°C for 30 min stirring, until a homogeneous and transparent solution was formed. The prepared DES was cooled and used for the catalysed Henry reaction without any purification.

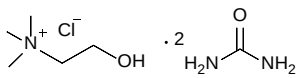
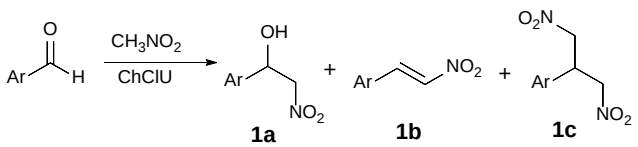


Figure 1 Structure of DES ChClU, also known as Reline (Choline Chloride/Urea 1:2)



Scheme 1 Model Henry reaction and possible products **1a-c**

From the reaction of a generic aromatic aldehyde with nitromethane, three different product can be obtained (Scheme 1): the expected nitroaldol adduct **1a**; the nitrostyrene derivative **1b**, resulting from dehydration of **1a**; the bis-adduct **1c**, obtained by the addiction of a second molecule of nitromethane on intermediate **1c**. In a first attempt, *p*-fluorobenzaldehyde was reacted with 5 equivalents of nitromethane in 10 equivalents excess of reline as solvent. To investigate the effect of temperature, the reaction was performed at 20°C (rt) and by heating at 50°C and 80°C. Results are reported in Table 1.

Table 1 Results of Henry reaction with *p*-fluorobenzaldehyde.

Entry	Temperature	Product[a] yield%[b]		
		1a	**1b**	**1c**
1	20°C	0	0	17
2	50°C	0	0	90
3	80°C	nd[c]	nd[c]	nd[n]

[a]Ar = *p*F-Ph. [b]Yield was evaluated by ^{1}H-NMR on the crude. [c]Formation of unidentified by-products

The results of Table 1 show the unprecedented finding that the Henry reaction can be driven to the dinitro-derivatives with excellent selectivity and conversion. Despite what was expected, the only product observed was **1c**. Neither the expected nitroaldol **1a** nor the elimination product **1b** was detected in the reaction crude. Compound **1c** is the result of a tandem Henry reaction/Michael addition between *p*-fluorobenzaldehyde and nitromethane. Firstly, **1a** is formed according to the classical Henry reaction; **1a** then spontaneously proceed to water elimination to produce the intermediate nitroolefin **1b** which then undergo a Michael addition of a second molecule of nitromethane to the double bond to afford the 1,3-dinitropropane derivative **1c**. This result is independent of the reaction temperature: at 20°C only **1c** is formed in 17% yield. At 50°C the 1,3-dinitropropane product is obtained in very good 90% yield after 24h. Increasing the temperature to 80°C for 24h produced an inseparable mixture of unidentified by-products: this outcome is mainly due to the extensive degradation of DES reline.

The high selectivity toward the synthesis of the 1,3-dinitropropane derivative is indeed very interesting. 1,3-dinitropropane derivatives are versatile building blocks, due to its versatile reactivity profile, which makes them ideal synthetic precursors amenable to functional and structural diversifications. Reduction of the nitro moiety produces 1,3 diamines, important structural motifs existing in many natural products and pharmaceuticals.[23] They are precursors of different targets such as heterocycles,[24] benzene derivatives,[25] carbohydrates,[26] and cyclohexane derivatives.[27] They have been also used as key building blocks for biologically active substances including a novel oxazolidinone antibacterial candidate.[28] Several examples for the synthesis of 1,3-dinitroalkanes have been described in the literature. The conventional synthesis of 1,3-dinitroalkanes is performed in basic condition through the Michael addition of nitroalkanes to nitroolefins under basic catalysis, usually affording the products

in low or moderate yields,[29] for the formation of ~~-~~polymeric byproducts. Efforts have been devoted to developing one-pot synthetic procedures starting from the aldehyde. Good results have been obtained in the presence of heterogeneous catalysts as basic alumina,[30] KF-$NaHCO_3$,[31] silica-alumina supported amines.[32] Alternatively, the use of different Ni-phosphine species[33] or electrochemical synthesis[34] has been reported.

Stimulated by this finding, we tried to improve the procedure to shorten the reaction time and to achieve higher yields. To this end, we investigated the use of unconventional microwave irradiation to heat the reaction mixture.

Microwave (MW) assisted chemistry can offer several advantages such as reduced processing time and energy costs with respect to~~concerning~~ conventional heating methods. In the MW-assisted chemical processing field, the use of strong MW absorbing solvents is mandatory. Additionally, physicochemical properties like high thermal stability and low vapour pressure are desirable due to the risks associated to the use of pressurize vessels.[35] DESs are in general good solvent for microwave heating[36] and reline, due its ionic nature and very low vapour pressure, is particularly suitable.

The influence of microwave irradiation in the reaction between nitromethane and *p*-fluorobenzaldehyde was thus investigated, starting with 5 equivalents of nitromethane in 10 equivalents excess of reline as solvent, at different temperature and reaction times. These studies aimed to achieve the highest yields in the shortest time. Results are reported in Table 2.

Table 2 MW-irradiated Henry reaction screening.

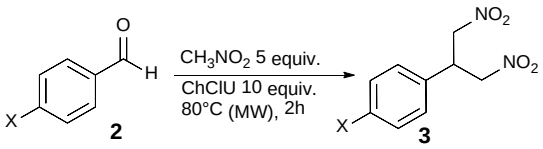
Entry	Temperature	Time	TEA (equiv.)	Product[a] yield%[b] 1a	1b	1c
1	50°C	1 h	0	0	0	9
2	80°C	2 h	0	0	0	96
3	50°C	2 h	5	38	0	58
4	80°C	2 h	5	29	0	72
5[c]	80°C	2 h	5	18	0	22

[a]Ar = pF-Ph. [b] Yield was evaluated by ^{1}H-NMR on the crude. [c] Reaction done with one equivalent of nitromethane.

At 50°C after 1h a poor 9% yield was obtained which turned into the satisfying 96% at 80°C after only 2h. It is worth mentioning that, although we reported the severe degradation of reline at 80°C (Table 2, entry 3), nonetheless the use of MW allowed to shorten the reaction time thus preserving the integrity of the DES (no degradation of reline was detected). In another experiment, we investigated the use of triethylamine (TEA) as an additional catalyst to facilitate the formation of the nitroaldol adduct, the first step toward the formation of the 1,3-dinitropropane derivative. When 5 equivalents of TEA were added, both at 50°C (entry 3) and 80°C (entry 4), **1a** was found in 38% and 29% yield respectively, together with **1c** as the major product (58% and 72% yield). This result suggests that the amine can interact with the DES in some way to depress its catalytic activity. The result is an evident decrease of the selectivity of the reaction. We then tried to completely switch the selectivity toward **1a** by using a stoichiometric amount of nitromethane (entry 5) but a mixture of **1a** and **1c** was produced. Interestingly, **1b** was not detected in any circumstances, thus suggesting that, once the nitroolefin is formed, the second addition of nitromethane is very fast.

We then explored the general applicability of our approach by treating different aldehydes in the optimized reaction conditions (Table 3).

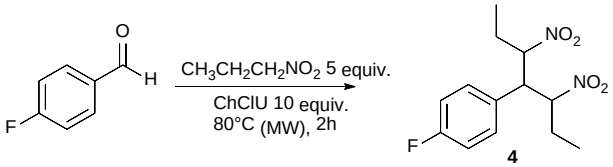
Table 3 Screening of the reaction with different aldehydes.



Entry	X	Product	Yield[a]
1	H	**3a**	96
2	NO_2	**3b**	98
3	Me	**3c**	70
4	Cl	**3d**	96
5	OMe	**3e**	55

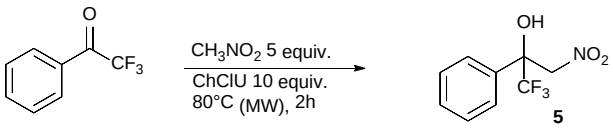
[a]Yield was evaluated by ^{1}H-NMR on the crude.

The 1,3-dinitropropane **3** was obtained as the only product in all the cases. This finding confirms the intrinsic selectivity of the Henry reaction in reline ~~DES~~ with MW irradiation. Quantitative yields were observed with benzaldehyde or electron-poor aromatic aldehydes (entries 1, 2 and 4). As expected, the presence of substituens with +I or +M electronic effect in conjugating position of the aromatic ring made the substrates less reactive leading to lower yields (entries 3 and 5).



Scheme 2. Reaction between *p*-fluorobenzaldehyde and nitropropane

When nitropropane was used instead of nitromethane, compound **4** was obtained in 88% yield as a *syn*/*anti* 1:1 mixture of diastereoisomers (Scheme 2).



Scheme 3. Reaction between nitromethane and trifluoromethylacetophenone

The reactivity toward ketones was also investigated. Usually, ketones are much less reactive than aldehydes. Nevertheless, good yields can be obtained from the Henry reaction with the activated trifluoromethylketones as substrates,[37] particularly with the use of MW.[38] We then reacted nitromethane with both benzophenone and trifluoromethylbenzophenone under optimized conditions. Significant yields were achieved only starting from the activated trifluoromethylbenzophenone

which produced the nitroaldol **5** in almost quantitative yield (Scheme 3). Anyway, no trace of the dinitro adduct was detected. Finally, a preliminary exploration of the role of HBA (choline chloride and choline acetate) and HBD (urea and glycolic acid) of DES in the outcome of the reaction was carried out. The possible combinations of ~~choline chloride and choline acetate with urea and glycolic acid~~the two components to form the DES are indicated in Table 4. The use of the DES of Table 4 is expected to provide a first indication on the influence of HBA and HBD on the selectivity and yields.

Table 4 DESs prepared for this study

Entry	HBA	HBD	Molar ratio	Abbreviation
1	Choline Chloride	Urea	1:2	ChClU
2	Choline Acetate	Urea	1:2	ChOAcU
3	Choline Chloride	Glycolic Acid	1:1	ChClGlyA
4	Choline Acetate	Glycolic Acid	1:1	ChOAcGlyA

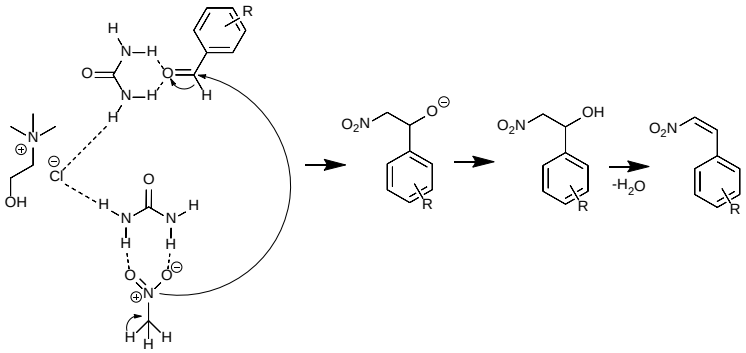
The results are summarized in Table 5. The replacement of chloride ions with acetate (ChOAcU, entry 2) lead to the obtainment of an unwanted mixture of by-products. We may propose that the presence of acetate ions could change the reaction mechanism and inhibit the selective formation of 1,3 dinitro compound. The tests on choline chloride-glycolic acid (ChClGlyA, entry 3) and choline acetate-glycolic acid (ChOAcGlyA, entry 4) confirmed the importance of the presence of urea for the catalytic ~~activity, since~~activity since no Henry~~-~~ adduct was observed. Interestingly, the use of ChOAcGlyA produced the partial oxidation of the aldehyde to the corresponding carboxylic acid. Studies on this result are ongoing in our laboratories.

Table 5. Study of the effect of DES in the model optimized reaction (nitromethane and *p*-fluorobenzaldehyde)

Entry	DES	Product (yield%)[a]
1	ChClU	**1c** (96%)
2	ChOAcU	mixture of byproducts
3	ChClGlyA	N.R.
4	ChOAcGlyA	p-fluorobenzoic acid (67%)

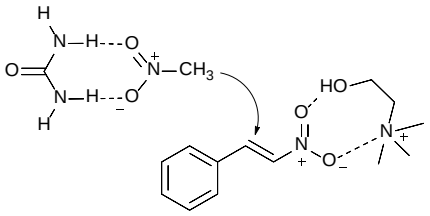
[a]Yield was evaluated by ^{1}H-NMR on the crude.

Urea-based catalysts are known to work in such reactions by hydrogen bonding catalysis.[39] On the bases of the results previously discussed, a possible mechanism for the formation of the 1,3-dinitropropane derivative can be postulated, as in Scheme 4. The first step, the formation of nitroaldol, occurs through a classical activation of nitromethane by coordination of the nitro group with urea, promoting the reaction and give beta-nitro alcohol compound (Scheme 4).[18] These hydrogen bonds increase the electrophilicity of carbonyl carbon atom and makes the methyl group of nitromethane more reactive.



Scheme 4 Proposed mechanism for Henry reaction in DES catalysed medium[18]

After the nitroolefin is formed by elimination of water, a possible and cooperative action of both the urea and the choline components of DES can be suggested to explain the high reactivity toward the formation of the 1,3-dinitropropane product. Choline can activate the nitroolefin by coordination involving both the ammonium and the hydroxy group as shown in Scheme 5 (similar mode of interactions has been yet observed in the solid state[39]).



Scheme 5. Proposed mode of activation by DES.

Conclusions

In conclusion, in this work we were able to realize an efficient and straightforward synthesis of symmetric 1,3-dinitropropanes by means of the combination of DES reline and MW irradiation. Products have been obtained in high yields for several aldehydes, both with nitromethane and nitropropane. The proposed approach seems to be less efficient with ketons, except for the activated trifluoro-methylbenzophenone which was converted into the nitroaldol adduct in almost quantitative yields. The reactions outcome seems to indicate a reaction mechanism with the involvement of both choline and urea to explain the high reactivity of the system. The serendipitous finding of excellent selectivity and yields of the Henry reaction under DES-MW conditions opened a mild, efficient and facile synthesis to challenging 1,3-dinitropropane derivatives.

Experimental

General information

All reagents and solvents were purchased from commercial sources and used without further purification. The reactions were carried out under atmospheric air.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer (^{1}H NMR, 400 MHz; ^{13}C NMR, 100MHz). The

spectra were registered at room temperature, otherwise indicated, in $CDCl_3$, with tetramethylsilane (TMS, δ = 0.0 ppm) used as the internal standard.

DESs preparation

DESs were prepared according to one of the most used procedure reported in the literature. Briefly, the preparation involved the combination of choline choline chloride (HBA) with urea or glycolic acid (HBDs), according to the molar ratio reported in Table 4, at 80°C for 30 min stirring, until a homogeneous and transparent solution was formed. The prepared DESs were cooled and used for our solubility tests without any purification. The water content of freshly DESs was determined using a Karl Fischer (KF) coulometric titrator from Mettler Toledo and was found equal to 0.96% for ChClU, 1.40% for ChClGlyA, 0.54% for ChOAcU and 0.74% for ChOAcGlyA.

General procedure for Henry reactions

In a typical procedure, the desired DES (10eq) was charged in a vessel of a 5 mL. Nitromethane or nitropropane(5eq) and the aldehyde or ketone (1 eq) were then added in one portion. At the end of reaction time, the mixture was extracted with dichloromethane (3x5mL). The collected organic phases were washed with water (2x 15ml) to eliminate the trace of DES. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude mixture was dissolved in $CDCl_3$ and analyzed with ^{1}H-NMR.

Acknowledgements

G.C.D. thanks Politecnico di Milano for her Inter-Departments PhD scholarship. The authors acknowledge Barbara Corsico Piccolino for help in experimental work.

Notes and references

1 1 N. Ono, *The Nitro Group in Organic Synthesis*, John Wiley & Sons, Inc., 2001. 1 G. Rosini and R. Ballini, *Synthesis (Stuttg).*, 1988, **1988**, 833–847.
2 L. Henry, *Bull. Acad. R. Belg*. 1896, **32**, 33
3 F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915–945.
4 (a) S. Saranya, N. A. Harry, S. M. Ujwaldev and G. Anilkumar, *Asian J. Org. Chem.*, 2017, **6**, 1349–1360. (b) C. Palomo, M. Oiarbide and A. Mielgo, *Angew. Chemie Int. Ed.*, 2004, **43**, 5442–5444. (c) C. Palomo, M. Oiarbide and A. Laso, *European J. Org. Chem.*, 2007, 2561–2574. (d) J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron Asymmetry*, 2006, 17, 3315–3326.
5 (a) T. Marcelli, R. N. S. Van Der Haas, J. H. Van Maarseveen and H. Hiemstra, *Angew. Chemie - Int. Ed.*, 2006, **45**, 929–931. (b) Y. Alvarez-Casao, E. Marques-Lopez and R. P. Herrera, *Symmetry (Basel).*, 2011, **3**, 220–245.
6 S. E. Milner, T. S. Moody and A. R. Maguire, *European J. Org. Chem.*, 2012, **2012**, 3059–3067.
7 M. Mokhtar, B. F. A. Alhashedi, H. A. Kashmery, N. S. Ahmed, T. S. Saleh and K. Narasimharao, *ACS Omega*, 2020, **5**, 6532–6544.
8 (a) T. Jiang, H. Gao, B. Han, G. Zhao, Y. Chang, W. Wu, L. Gao and G. Yang, *Tetrahedron Lett.*, 2004, **45**, 2699–2701. (b) R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo and L. Vaccaro, *Green Chem.*, 2007, **9**, 823–838.
9 R. S. Vanna, R. Dahiya and S. Kumar, *Tetrahedron Lett.*, 1997, **38**, 5131–5134.
10 (a) L. Vaccaro, *European J. Org. Chem.*, **2020**, DOI:10.1002/ejoc.202000131. (b) C. J. Clarke, W. C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800.
11 (a) Q. Zhang, K. De Oliveira Vigier, S. Royer and F. Jérôme, *Chem. Soc. Rev.*, 2012, **41**, 7108–7146. (b) A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis and A. R. C. Duarte, *ACS Sustain. Chem. Eng.*, 2014, **2**, 1063–1071
12 A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142–9147.
13 E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 11060–11082.
14 S. Khandelwal, Y. K. Tailor and M. Kumar, *J. Mol. Liq.*, 2016, **215**, 345–386.
15 C. M. A. Brett, *Curr. Opin. Electrochem.*, 2018, **10**, 143–148.
16 D. V. Wagle, H. Zhao and G. A. Baker, *Acc. Chem. Res.*, 2014, **47**, 2299–2308.
17 Y. P. Mbous, M. Hayyan, A. Hayyan, W. F. Wong, M. A. Hashim and C. Y. Looi, *Biotechnol. Adv.*, 2017, **35**, 105–134.
18 S. C. Cunha and J. O. Fernandes, *TrAC - Trends Anal. Chem.*, 2018, **105**, 225–239.
19 A. Shishov, A. Bulatov, M. Locatelli, S. Carradori and V. Andruch, *Microchem. J.*, 2017, **135**, 33–38.
20 B. S. Singh, H. R. Lobo and G. S. Shankarling, *Catal. Commun.*, 2012, **24**, 70–74.
21 X. Tian, S. Zhang and L. Zheng, *J. Microbiol. Biotechnol.*, 2015, **26**, 80–88.
22 (a) R. Pedrosa, J. M. Andrés, D. P. Ávila, M. Ceballos and R. Pindado, *Green Chem.*, 2015, **17**, 2217–2225. (b) P. Borah, J. Mondal and Y. Zhao, *J. Catal.*, 2015, **330**, 129–134.
23 X. Ji and H. Huang, *Org. Biomol. Chem.*, 2016, **14**, 10557–10566.
24 F. C. Escribano, M. P. Derri Alcántara and A. Gómez-Sánchez, *Tetrahedron Lett.*, 1988, **29**, 6001–6004.
25 (a) R. Ballini, L. Barboni, D. Fiorini, G. Giarlo and A. Palmieri, *Chem. Commun.*, 2005, 2633–2634. (b) R. Ballini, L. Barboni, C. Femoni, G. Giarlo and A. Palmieri, *Tetrahedron Lett.*, 2006, **47**, 2295–2297. (c) D. Y. Park, K. Y. Lee and J. N. Kim, *Tetrahedron Lett.*, 2007, **48**, 1633–1636.
26 D. P. Pham-Huu, M. Petrušová, J. N. BeMiller and L. Petruš, *Tetrahedron Lett.*, 1999, **40**, 3053–3056.
27 (a) R. Ballini, L. Barboni, D. Fiorini, G. Giarlo and A. Palmieri, *Green Chem.*, 2005, **7**, 828–829. (b) Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell and K. A. Jørgensen, *Angew. Chemie Int. Ed.*, 2007, **46**, 9202–9205. (c) L. Liu, Y. Cotelle, A. J. Avestro, N. Sakai and S. Matile, *J. Am. Chem. Soc.*, 2016, **138**, 7876–7879.
28 T. Yang, J. X. Chen, Y. Fu, K. Chen, J. He, W. Ye, Z. Sang and Y. Luo, *Org. Process Res. Dev.*, 2014, **18**, 511–519.
29 (a) P. Bora, P. P. Bora, B. Wahlang and G. Bez, *Can. J. Chem.*, 2017, **95**, 1261–1266. (b) C. Rabalakos and W. D. Wulff, *Synlett*, 2008, **2008**, 2826–2830.
30 R. Ballini, G. Bosica, D. Fiorini and A. Palmieri, *Synthesis (Stuttg).*, 2004, **2004**, 1938–1940.
31 A. Fierro, M. C. Rezende, S. Sepúlveda-Boza, M. Reyes-Parada and B. K. Cassels, *J. Chem. Res.*, 2001, **2001**, 294–296.
32 K. Motokura, M. Tada and Y. Iwasawa, *Angew. Chemie Int. Ed.*, 2008, **47**, 9230–9235.
33 M. Gao and Y.-P. Wei, *J. Chem. Res.*, 2013, **37**, 146–148.

34 Z. I. Niazimbetova, D. H. Evans, L. M. Liable-Sands and A. L. Rheingold, *J. Electrochem. Soc.*, 2000, **147**, 256.
35 (a) D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563–2591. (b) J. M. Kremsner, A. Stadler and C. O. Kappe, *Microwave Methods in Organic Synthesis*, 2006, vol. 266.
36 (a) J. González-Rivera, E. Husanu, A. Mero, C. Ferrari, C. Duce, M. R. Tinè, F. D'Andrea, C. S. Pomelli and L. Guazzelli, *J. Mol. Liq.*, 2020, **300**, 112357. (b) V. Migliorati, F. Sessa and P. D'Angelo, *Chem. Phys. Lett. X*, 2019, **2**, 100001.
37 (a) F. Tur and J. M. Saá, Org. Lett., 2007, **9**, 5079–5082. (b) A. Das, M. K. Choudhary, R. I. Kureshy, K. Jana, S. Verma, N. U. H. Khan, S. H. R. Abdi, H. C. Bajaj and B. Ganguly, *Tetrahedron*, 2015, **71**, 5229–5237.
38 C. Gan, X. Chen, G. Lai and Z. Wang, *Synlett*, 2006, **2006**, 387–390.
39 J. L. Wardell and E. R. T. Tiekink, *Acta Crystallogr. Sect. E Crystallogr. Commun.*, 2018, **74**, 1735–1740.

