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A more sustainable and efficient access to IMe_s-HCl and IPr-HCl by ball-milling

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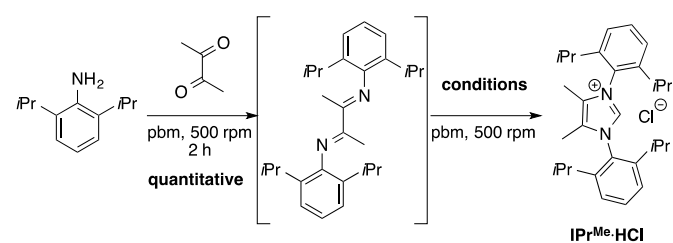
Herein is described a mechanochemical one-pot two-step procedure giving access to various NHC (*N*-heterocyclic carbene) precursors. This original approach enabled to produce the widely used IPr-HCl, IMe_s-HCl, Io-Tol-HCl and ICy-HCl in much better yields than conventional solvent-based procedures, while the environmental impact was drastically reduced.

In the past years, mechanochemistry, and more specifically ball-milling, has become an outstanding tool to facilitate the formation of numerous compounds,¹ including organic and organometallic molecules² as well as inorganic materials.³ Interestingly, this approach also enabled the access to compounds unattainable using classical solution chemistry.⁴ Ball-milling allows for a perfect mixing of the reactants under solvent-free or solvent-less conditions,⁵ thereby enabling enhanced reaction rates. We recently contributed to the field with the report of general, rapid and user-friendly solvent-less methods to generate [AgX(NHC)] (X = Br, Cl),⁶ [Ag(NHC)₂]Y (Y = BF₄⁻/PF₆⁻)⁷ as well as [CuCl(NHC)] and [Cu(NHC)₂]Y (Y = BF₄⁻/PF₆⁻)⁸ complexes by using a ball-mill (NHC = *N*-heterocyclic carbene). During these studies we showed that ball-milling alkyl halides with imidazoles provided *N,N*-dialkylimidazolium salts with better results than literature.^{6b} We thus envisioned that mechanochemistry could also be beneficial to the synthesis of *N,N*-diarylimidazolium salts,⁹ whose corresponding NHC are widely used as efficient ligands for catalysis,¹⁰ for instance in Grubbs-like¹¹ and PEPPSI-like catalysts.¹²

We first decided to focus on implementing user-friendly milling conditions through a step of 1,4-diazadiene (DAD) formation followed by cyclization using a C₁ carbon source to furnish the corresponding imidazolium salts. In order to find the best conditions that could be applied to a wide panel of imidazolium salts, this strategy was first applied to the synthesis of the challenging IPr^{Me}-HCl (1,3-bis(2,6-diisopropylphenyl)-4,5-dimethyl-1*H*-imidazol-3-ium chloride). Indeed, this sterically hindered imidazolium salt is obtained in relatively low overall yield in literature, 75% on the first step and 14-40% yield in the second step.¹³ Those yields could be improved to 91% and 77%, respectively, with the use of large quantities of anhydrous or distilled solvents in both steps.¹⁴ In addition, the first step required overnight reaction in an alcoholic solvent and subsequent isolation of the DAD upon precipitation. Of note, solvent-free DAD formation was already described previously,¹⁵ yet the use of mortar and pestle to perform the reaction hampered repeatability and scale-up perspectives. Imine formation was also already studied in the

solid-state.¹⁶ In our hands, milling 2,6-diisopropylphenylamine and 2,3-butanedione (1.0 eq.) for 2h in a zirconium oxide 20 mL jar [filled with 80 x 5 mm diameter ZrO₂ balls agitated at 500 rpm in a planetary ball-mill (pbm)] furnished the corresponding DAD in quantitative yield. This was confirmed by IR analysis of the reaction mixture and by the characteristic yellow colour of the reaction mixture. As perfect stoichiometry of reagents was used and full conversion was obtained in the first step, DAD could be directly engaged in the cyclization step, thereby avoiding any solvent incompatibility between the two steps.

The cyclization step revealed more challenging and a thorough optimization of conditions was necessary (Table 1). Different carbon sources were first evaluated, namely chloromethyl ethylether, formaldehyde, 1,3,5-trioxane and paraformaldehyde (Table 1, entries 1-4). The best result was obtained with paraformaldehyde together with 4M HCl in dioxane, furnishing IPr^{Me}-HCl in 49% yield over the two steps (Table 1, entry 4). Other activating agents were tested in the presence of paraformaldehyde. Changing HCl in dioxane for HCl in water or less acidic NH₄Cl prevented the isolation of any traces of the imidazolium salt, even after 6h of milling (Table 1, entries 5 and 6). *Tert*-butyldimethylsilyl chloride (TBDMSCl) and PCl₃ resulted in lower yields of 18-20% (Table 1, entries 7 and 8). Besides, using Lewis acidic aluminum chloride resulted in a poor 6% yield (Table 1, entry 9). As water formed during the course of the reaction could hydrolyze DAD, magnesium sulfate was added during the cyclization step to trap these water molecules. Unfortunately, it did not improve the final yield (Table 1, entry 10). Besides, adding MgSO₄ during the first step completely inhibited DAD formation. An efficient methodology reporting the selective formation of unsymmetrical imidazolium salts proved that the addition of zinc chloride was beneficial to the outcome of the reaction.¹⁷ However, in the ball-mill, adding ZnCl₂ did not improve the final yield, albeit IPr^{Me}-HCl was isolated in 45% yield (Table 1, entry 11). Finally, the best conditions were to use paraformaldehyde and 4M HCl in dioxane. After only 5h of milling (2h imine formation + 3h cyclization), the desired IPr^{Me}-HCl could be obtained in 49% yield, without isolating the DAD intermediate. In addition, the imidazolium salt was recovered upon precipitation in ACS grade EtOAc, which is considered in solvent classifications as a preferred and environmentally friendly solvent,¹⁸ and much preferable to THF which is the most frequently used solvent in solution-based approaches.

Table 1. Optimization of the milling conditions for the cyclisation step^a


Entry	Reagent (equiv.)	Additive (equiv.)	t (h)	Yield (%)
1	(1)	-	3	18
2	(1) ^b	HCO ₂ H (1) NaCl (1)	3	0
3	(0.33)	HCl ^c (1)	3	0
4	(1)	HCl ^c (1)	1 3	32 49
5	(1)	HCl ^d (1)	6	0
6	(1)	NH ₄ Cl (1)	3	0
7	(1)	TBDMSCl (1)	1	18
8	(1)	PCl ₃ (1)	3	20
9	(1)	AlCl ₃ (1)	3	6
10	(1)	HCl ^c (1) MgSO ₄ (1.9)	3	4
11	(1)	ZnCl ₂ (1) ^e HCl (1) ^c	3	45

^a Reaction conditions for the first step: 2,6-diisopropylphenylamine (2 equiv.), 2,3-butanedione (1 equiv.), pbm 500 rpm, 2h, total mass of reagents: 283.4 mg; isolated yields are given. ^b formaldehyde (37% in water) was used. ^c 4M HCl in dioxane was used. ^d 37% HCl in water was used. ^e ZnCl₂ was milled with DAD for 30 min, and then HCl was added. Mixture was stirred for an additional 2.5 h.

Of note, dioxane used in the ball-milling experiments represented much lesser amounts of solvents when compared to solvent-based conditions. Indeed, the η ratio (defined as the volume of liquid to the total mass of solid reactants)¹⁹ was of 0.5 while in solvent-based conditions this ratio is much generally over 10.20 To our opinion, even though the overall yield is not better than the best yields reported in literature, the milling conditions are more user-friendly since i) apart from very small amounts of dioxane, no reaction solvent was

used and thus no distillation of solvent is required, ii) inert atmosphere is not required, iii) reaction times are shorter, iv) the only solvent used for the recovery of the final pure compound is EtOAc that is considered as a preferred solvent.¹⁸

These one-pot conditions were then applied to the synthesis of several imidazolium salts commonly used as NHC precursors (Table 2). To our delight, **IMes·HCl** could be obtained in excellent yield (84%) using the milling technique (Table 2, entry 1), surpassing classical solvent-based synthesis. Of note, DAD formation, with the use of glyoxal, required the addition of catalytic amount of formic acid. The cyclization step was also attempted directly from corresponding and previously isolated DAD furnishing **IMes·HCl** in 87% yield after milling for 3h. This result demonstrated that in literature conditions the isolation of the DAD, which is compulsory because of solvent incompatibility issues between the two steps, is detrimental to the overall yield. The more sterically hindered analog **IMes^{Me}·HCl** was isolated in 66% (Table 2, entry 2). In comparison, two-step procedure in solution through DAD gave at best 12% overall yield, the best yield of 77% being obtained with an alternative strategy through formamidine formation and subsequent reaction with 3-halobutan-2-one.²¹ However, this strategy, even if providing the imidazolium salt in good yield, required a complicated set-up of reaction and further purification through silica gel chromatography. Gratifyingly, the widely used **IPr·HCl** was produced in quantitative yield by using our approach (Table 2, entry 3), while it was isolated in only 69% overall yield in solution with prolonged reaction times. Increasing the milling load to scale-up the reaction resulted in a lowered yield of 25%, due probably to homogenization problem in the jar. This optimization is currently under study in our lab. On the opposite, attempts to obtain the extremely hindered **IPr^{*}·HCl** were unsuccessful (Table 2, entry 5). While the DAD formation was not a problem in the pbm, the cyclizing step induced the formation of unidentified side-products as well as products resulting from the hydrolysis of the DAD under acidic conditions. Using aniline, *p*- and *o*-methyl aniline revealed successful and corresponding imidazolium salts **IPh·HCl**, **IP-Tol·HCl**, **IO-Tol·HCl**, could be isolated in 90, 80 and 95% yields, respectively (Table 2, entries 6, 7 and 9). It is important to note that their synthesis in solution was not precisely documented or required the catalytic quaternization of imidazole with phenyl boronic acid to obtain a good yield.²² However, the formation of **IP-Tol^{Me}·HCl** was unsuccessful probably due to a suspected low stability of the corresponding DAD under ball-milling conditions (Table 2, entry 8). Finally, widely used **ICy·HCl**, featuring alkyl groups on the nitrogen atoms, was also synthesized efficiently using the milling one-pot sequence (Table 2, entry 10). In comparison, its synthesis in solution required prolonged reaction times, the use of toxic solvent such as dichloromethane or toluene.

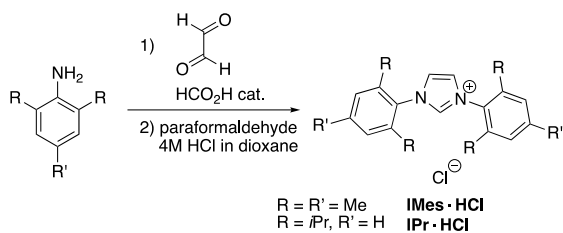
Table 2. Milling conditions for the synthesis of imidazolium salts^a

Entry	Compound	R ²	Overall yield (%) ^b	Conditions from lit. for i) DAD formation and ii) cyclization	Yield from lit. (%) ^c
1		H	84 (87)	i) <i>n</i> PrOH, 60-70°C, 80%. ²³ ii) TMSCl, (CH ₂ O) _{<i>n</i>} , 70°C, 2h, 86%. ²⁴	69
2		Me	66 (60)	i) Formic acid cat. in ethanol, 15h, 39%, ii) 15h, 31%. ^{14b} Through formamide: CH ₃ CN, 110°C, 20h, then toluene, Ac ₂ O, HCl, 90°C, 13.5h. ²¹	12 77
3		H	100 (98)	i) Formic acid cat. in methanol, 15h, 90% ii) 16h, 65-75%. ²⁵	68
4		Me	49 (55)	i) Anhydrous conditions, 75-91%. ^{14b, 15} ii) Second step: 77%. ^{14a}	69
5		H	0	i) MgSO ₄ , CH ₂ Cl ₂ , 4 days, 90%. ii) HCl/ZnCl ₂ /(CH ₂ O) _{<i>n</i>} , 1.5h, 60%. ²⁶	54
6		H	90	Quaternization of imidazole with PhB(OH) ₂ : DMF, 100°C, 10h, 92%. ²²	92
7		H	80	One-pot procedure: anhydrous toluene, 100°C, 2h. ²⁷	n.r. ^d
8		Me	0	n.r. ^d	n.r. ^d
9		H	95	n.r. ^d	n.r. ^d
10		H	80	i) CaCl ₂ , CH ₂ Cl ₂ , 80%. ²⁸ ii) AcCl, CH ₂ (NMe ₂) ₂ , CH ₂ Cl ₂ , 82%. ²⁸ One-pot synthesis: (CH ₂ O) _{<i>n</i>} /HCl, toluene, 16h. ²⁹	66 75

^a Reaction conditions: amine (2 equiv.), butadione or glyoxal 40% in water (0.642 mmol, 1 equiv.), HCO₂H (1-3 drops if glyoxal was used), pbm 500 rpm, 2h, then addition of paraformaldehyde (1 equiv.) in 4M HCl in dioxane (1 equiv.), pbm, 500 rpm, 3h. ^b The yield of the second step is given in brackets. ^c Best overall yield found in literature. ^d n.r. = not reported.

To assess the sustainability of our one-pot solvent-less procedure, the *E* factor³⁰ and ecoscale score³¹ were calculated for the synthesis of the widely used **IMes-HCl** and **IPr-HCl**, using literature as a reference as well as home-made experiments, using the same conditions as in the ball-mill, for solution chemistry (Table 3).²⁵ Among the different green metrics, the *E* factor was evaluated since solvent use, including water, highly contributes to the environmental impact of an organic synthesis. Ecoscale score is complementary to *E* factor since it takes into account toxicity of reagents and solvents used. Gratifyingly, the values calculated from the ball-mill procedure data (Table 3, entry 1) are much better than those obtained using solution chemistry in the same conditions

(Table 3, entry 2) or using the best results from literature (Table 3, entry 3), indicating a more sustainable procedure. In particular, *E* factor values of 1.5 and 0.9 were obtained using the ball-mill, which is more than 5 times lower than the values calculated from solution chemistry and literature data. These differences could be explained by the lowering of the amount of solvent used with a concomitant improvement of the overall yield. The ecoscale scores follow the same trend, with higher values for ball-milling than for solution-based synthesis, thus proving the positive environmental impact of mechanochemistry on the synthesis of **IMes-HCl** and **IPr-HCl**.

Table 3. *E* Factor and ecoscale score evaluation for **IMes-HCl** and **IPr-HCl** synthesis^a

Entry	Method	<i>E</i> Factor		Ecoscale score	
		IMes-HCl	IPr-HCl	IMes-HCl	IPr-HCl
1	Ball-mill ^b	1.5	0.9	56	62
3	Solution ^c	16.4	48.6	22	12
2	Lit. ^d	16.6 ²³⁻²⁴	4.9 ²⁵	10	27

^a See SI for details. ^b Results from Table 2, entry 3. ^c Results from experiments performed in our laboratory. See SI for details. ^d Results calculated with data from literature.

Conclusions

In summary, we developed a solvent-less mechanochemical one-pot two-step procedure to obtain NHC precursors directly from anilines. Importantly, the milling methodology allowed to significantly improve the yields for widely used **IPr-HCl**, **IMes-HCl**, **Io-Tol-HCl** and **ICy-HCl** syntheses when compared to literature procedures. Concomitantly, the *E* factor and ecoscale score for this milling procedure were dramatically better than for solvent-based procedures. This methodology allowed to avoid the isolation of DAD intermediates and to reduce DAD hydrolysis. It also enabled to prevent solvent compatibility issues between the two synthetic steps that are sometimes observed when using a solution-based strategy. This methodology was found quite efficient, with a facilitated set-up, solvent-less conditions and short reaction times, for the synthesis of imidazolium salts featuring aryl or alkyl substituents on the nitrogen atoms as well as hydrogen and methyl groups on the imidazole backbone.

Conflicts of interest

There are no conflicts to declare.

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