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A highly sustainable route to pyrrolidone derivatives – direct access to biosourced solvents†

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Access to a series of 5-methylpyrrolidone derivatives is described directly using the biosourced levulinic acid in the absence of any additive, catalyst or solvent. The highly selective reaction proceeds with an *E*-factor as low as 0.2. Products are recovered in very good yields after a simple distillation.

The replacement of toxic, non-renewable fossil solvents is one of the main scientific challenges both in industry and academia. As an example, the massive use of solvent explains the poor E-factor of the fine or pharmaceutical industry and some of the most common solvents are now part of the REACH[1] "Substances of Very High Concern" list (*i.e.* NMP, DMF, DMAc, *etc.*).[2] Thus, the development of environmentally benign alternatives has become a priority.[3] The use of platform molecules available from biomass constitutes a very promising solution as it opens a new field of enormous potential impact for the chemical supply chain. In addition, the development of new bio-based solvents constitutes an opportunity for investigating new routes for the development of chemicals displaying better toxicological or ecotoxicological profiles.

Levulinic acid (LA) is among the most promising chemicals produced from biomass feedstock.[4] It is produced generally by the acidic hydrolysis of carbohydrates.[5] LA is a platform molecule that can be used for numerous chemical applications such as the synthesis of γ-valerolactone (GVL) already used as a fuel additive or solvent.[6] LA can also be converted to *N*-substituted-5-methyl-pyrrolidones (*N*-substituted-5-MeP) by reductive amination and cyclisation.[7–9] *N*-substituted-5-MeP are structurally related to the well-known *N*-methylpyrrolidone (NMP) that was recently implemented in the "Substance of Very High Concern" list by the European Chemical Agency (EChA) and that is under discussion for restriction in its use.[10] Of note is that NMP is a mild-volatile and thermally stable chemical, widely used in industries as a solvent for applications such as the synthesis of plastic and resin polymers, extraction of aromatics in oil processing, as a cleaning agent of silicon wafers, *etc*. Thus, its production is estimated to be 200 000–250 000 tons per year.[11] Accordingly, considering the vital relevance of NMP in numerous industrial applications, finding alternatives to NMP is a priority. Among the potential alternatives for NMP, the use of fuel-based solvents such as DMSO (dimethylsulfoxide), NEP (*N*-ethylpyrrolidone), DMF (dimethylformamide) or DMAc (dimethylacetamide) was proposed. However, they do not display performances comparable to NMP and several of them are carcinogenic. Yet, new solvents are still highly desired.

N-Substituted-5-MeP can be considered as the closest analogue of NMP available from biomass. The synthesis of 5-methyl-pyrrolidones from LA was first reported using heterogeneous catalysis and dihydrogen as the reducing agent by Shilling,[12] Crook,[13] and more recently by Manzer *et al.*[14] Thus, Manzer *et al.* describe the need for different transition-metals such as Ni, Cu, Rh, Ru, Ir or Pt, grafted on silica, alumina or carbon as potential heterogeneous catalysts. Later on, Huang *et al.*[9] reported a synthesis of *N*-alkyl-5-methylpyrrolidones involving LA and primary amines using the [Ru]-catalyzed decomposition of formic acid (FA). In addition to the use of an expensive metal catalyst, air-sensitive electron-rich phosphine-ligands such as $P(t\text{-Bu})_3$ or $P(Cy)_3$ were also required for ensuring a good conversion. Very recently, a procedure requiring several equivalents of DMSO as an additive and a tertiary amine was reported.[8b] The DMSO/tertiary amine system was described as an activating combination for promoting the decomposition of FA and was proposed as an alternative to metal-based catalysis. However, this procedure requires critical purification steps in order to remove all additives, solvents as well as the unreacted starting material. Comparison of *E*-factors[15] for some of these reported procedures shows that catalysis is preferable over the use of a large amount of additives in terms of wastes and environmental footprint (Table 1).

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† Electronic supplementary information (ESI) available: Detailed synthetic procedure and spectral characterization of the synthesized pyrrolidones. See DOI: 10.1039/c5gc00417a

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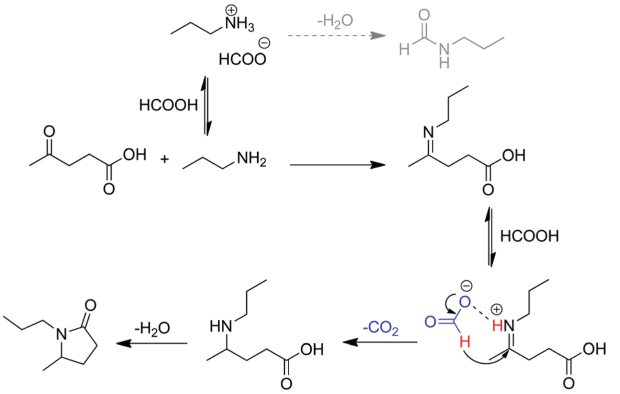
Table 1 Comparison of the *E*-factors from common procedures for the synthesis of 5-methyl-*N*-cyclohexylpyrrolidone

Entry	Promoter	*E*-factor (kg waste per kg product)	Reference
1	Ruthenium catalysis	90	9
2	Activating agents	199	8
3	Heterogeneous platinum catalysis	66	7
4	**None**	**0.2**	**This work**

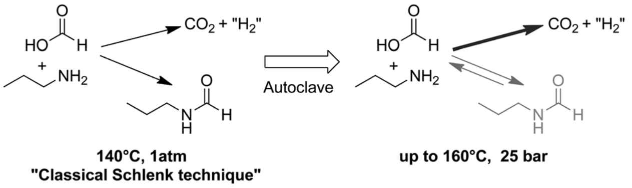
Although the recent developments allow the synthesis of a wide range of *N*-substituted-5MeP derivatives in reasonable to very good yields, the use of metal-catalysts, activating agents and solvents as well as purification steps still constitute strong limitations in terms of costs and environmental footprint. Herein, we report a new and simple process for the synthesis of *N*-substituted-5-MeP derivatives which overcomes most of these above-mentioned limitations, hence affording a very advantageous *E*-factor value.[16]

Within the frame of our efforts to develop an environmentally friendly, industrially applicable synthesis of the 5-methyl-*N*-propylpyrrolidone (5Me-NPP) **2a**, we re-investigated the Ru-catalyzed approach by Huang *et al.*[9] Aiming at developing an air and moisture tolerant catalyst, we considered first the combination of $[Ru(p\text{-cymene})Cl_2]_2$ and $(o\text{-tolyl})_3P$ as a catalytic system for promoting the reductive amination of LA by *N*-propylamine in the presence of FA (Table 2).

Interestingly, under argon at normal pressure and in the absence of a solvent, we discovered that decreasing strongly the catalyst loading did not influence drastically the outcome of the reaction. Indeed, **2a** was still formed in decent amounts even in the presence of 0.05 mol% catalyst (Table 2, entries 1–3). More interestingly, when the reaction was carried out in the absence of a catalyst[17], **2a** was still obtained in 56% yield along with the formamide **3a** and H_2O (Table 2, entry 4). Actually, this result is consistent with the well-known Leuckart–Wallach (LW) type mechanism (Scheme 1).[18]



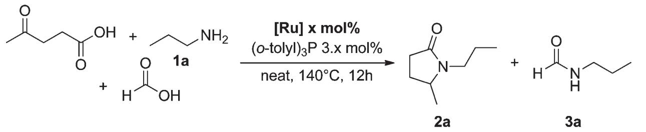
Scheme 1 Leuckart–Wallach mechanism and formation of the formamide byproduct.



Scheme 2 Limitation of the formamide formation under autogenous pressure.

As depicted in Scheme 1, formic acid is formally converted to CO_2 and "H_2" through the hydrogenation of the imine function, initially formed *in situ* from LA and propylamine. The synthesis of formamides through this process is known to be reversible in the presence of water.[19] However, increasing the reaction time had no effect on the formation of **2a** or on the hydrolysis of **3a**. Interestingly, this limitation was overcome by performing the reaction in an autoclave (Scheme 2).

Table 2 Effect of the catalyst loading[a]



Entry	[Ru] mol%	Conversion[b] (%)	**2a** : **3a**
1	1	86	1 : 0
2	0.5	72	4 : 1
3	0.05	58	6 : 4
4	**0**	**56**	**11 : 9**

[a] The ratio LA/FA/**1a** is 1 : 1 : 1. [b] Determined by ^1H NMR.

Indeed, in an isochoric system, the production of CO_2 and H_2 from the decomposition of FA allowed production of the desired pyrrolidone **2a** as the only product. A maximum pressure of 25 bars after 4.5 h was obtained. Interestingly, a pressure monitor can be used for determining the progress of the reaction assuming that CO_2 follows the ideal gas law (H_2 is consumed for the reduction of the imine function). Indeed the quantity of CO_2 released at full conversion corresponds to the theoretical pressure calculated from the decomposition of FA (Fig. 1). As predicted, **2a** was obtained quantitatively in 4.2 h at 25 bar for a temperature set at 160 °C[20] (for details of calculations see the ESI†). Using these conditions, **2a** was isolated as an almost pure compound. A simple distillation afforded pure **2a** as a colourless liquid in 84% isolated yield.

Furthermore, by setting parameters according to the ideal gas law, the reaction could be performed at higher pressure and temperature, thus shortening the reaction time.[21] (see the ESI†).

Various *N*-substituted-5MeP were synthesised from LA, FA and several amines (Table 3). Preferentially, we chose aliphatic

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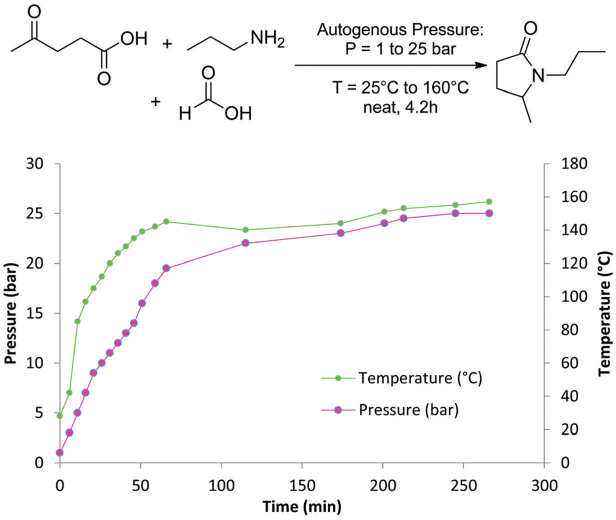
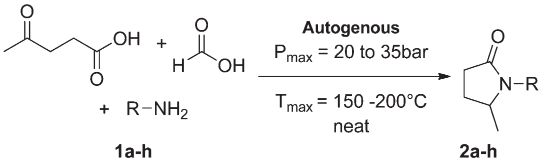


Fig. 1 Evolution of the temperature and self-generated pressure for the synthesis of **2a**. The ratio LA/FA/**1a** is 1 : 1 : 1. The maximal pressure of 25 bar corresponds to 100% conversion of FA at 160 °C.

Table 3 Scope and limitation of the reaction[a]



Entry	Amine R=	Conversion[b] (%)	Product	Yield[c] (%)
1	*n*-Propyl (**1a**)	>99	5MeNPP (**2a**)	84
2	*n*-Butyl (**1b**)	>99	5MeNBP (**2b**)	82
3	i-Propyl (**1c**)	>99	5MeNiPP (**2c**)	80
4	i-Butyl (**1d**)	>99	5MeNiBP (**2d**)	86
5	*t*-Butyl (**1e**)	—	5MeNtBP (**2e**)	—
6	Cyclohexyl (**1f**)	89	5MeNChP (**2f**)	88
7[d]	*n*-Octyl (**1g**)	86	5MeNOP (**2g**)	80
8[d]	Benzyl (**1h**)	>99	5MeNBzP (**2h**)	49

[a] Conditions: 60–150 mmol scale, ratio LA/FA/**1a–h**: 1 : 1 : 1. [b] Determined by ^1H NMR. [c] Isolated yield after distillation. [d] Isolated yield after extraction.

amines having a low boiling point and viscosity in order to obtain potential NMP alternatives for solvent applications. Using our optimized conditions, aliphatic (iso)propyl- and (iso)butylamines **1a–d** reacted with full conversion (Table 3, entries 1–4). The resulting pyrrolidones **2a–d** were purified by distillation under reduced pressure and isolated in 80–86% yield. The difference between the conversion and the yield is attributable to some loss during the distillation process that was realized on a laboratory scale (60–150 mmol). Cyclohexyl- and *t*-butylamines **1e** and **1f** displayed different reactivities depending on the steric hindrance of the amine. Indeed, using our mild conditions, the *t*-butylamine did not afford the corresponding pyrrolidone (5MeNtBP was not reported even in the presence of a catalyst or activating agents),[8,9] but interestingly **1f** afforded **2f** in 88% isolated yield (Table 3, entries 5 and 6). Because of its higher viscosity, *n*-octylamine **1g** also displayed a lower reactivity (conv. 86%). However, a remarkable 80% yield was obtained after purification. Of note is that due to their higher boiling points, **2g** and **2h** were isolated by liquid–liquid extraction using EtOAc and a saturated NH_4Cl solution (Table 3, entries 7 and 8). However, **2h** was isolated in a moderate 49% yield because of its partial solubility in water.

Conclusions

In conclusion, we have developed a very efficient and environmentally friendly procedure to synthesize and produce *N*-substituted-5-methylpyrrolidone derivatives. Advantageously, our methodology does not require any metal catalyst, additive or special care (anhydrous or oxygen free conditions) for affording the expected pyrrolidones in a very efficient way. In addition, monitoring the evolution of the pressure over time allows an easy follow up of the reaction. Interestingly, as moderate pressures are used, this methodology could certainly be developed at the industrial scale without any significant cost increase. Accordingly, a series of *N*-substituted pyrrolidones was prepared. These unprecedented results clearly demonstrate the efficiency of our approach that allows the synthesis of potential NMP solvent substitutes from the biosourced levulinic acid with an exceptional *E*-factor of 0.2.

General experimental procedure

An autoclave equipped with a manometer, a safety valve and a thermometer was charged with levulinic acid (1 equiv.). Next, the amine (1 equiv.) was slowly added using a syringe followed by formic acid (1 equiv., exothermic reaction). When all reagents were added, the reactor was sealed and the reaction runs for 3–10 h at 160–200 °C upon monitoring the pressure and the temperature. Then, the reaction was allowed to cool to room temperature before the reactor was degassed and slowly opened. The crude pyrrolidone was collected as an orange to brown liquid. Depending on the nature of the amine, the crude product was washed with a dilute aqueous solution of Na_2CO_3, and extracted with AcOEt. The separated organic layer was washed with brine, and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired compounds. In the case of the volatile amine (bp < 100 °C), a distillation under pressure was carried out and afforded a clear oil.

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1 REACH = Registration, Evaluation and Authorization of Chemicals Regulation.

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17 Reactions were repeated in new, metal-free glassware and reactors.

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20 Reaction conditions for a maximum pressure of 25 bar: total volume 100 mL, FA 60 mmol, LA/FA/**1a**: 1 : 1 : 1, temperature 160 °C (for details, see the ESI†).

21 Reaction conditions for a maximum pressure of 64 bar: total volume 100 mL, FA 120 mmol, LA/FA/**1a**: 1 : 1 : 1, temperature 200 °C (for details, see the ESI†).

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