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COMMUNICATION

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 from 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 in academia. As an example, solvents account for a major part in the very high environmental factor of the fine or pharmaceutical industry and some of the most common solvents are now part of the REACH¹ “Substances of Very High Concern” List (i.e. NMP, DMF, DMAc...)² Thus, the development of environmentally benign alternatives has become a priority.³ The use of platform molecules available from the biomass constitutes a very promising solution as it opens a new field of enormous potential impacts 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 chemical 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 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 use restriction.¹⁰ Of note, NMP is a mild-volatile and thermally stable chemical, widely used in industries as solvent for applications such as the synthesis of plastic and resin polymers, extraction of aromatics in oil processing, cleaning agent of silicon wafers, etc.. Thus, its production is

estimated to 200,000 – 250,000 tons/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, fuel-based solvent such as DMSO (dimethylsulfoxide), NEP (N-ethylpyrrolidone), DMF (dimethylformamide) or DMAc (dimethylacetamide) were proposed. However, they do not display performances comparable with 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-methylpyrrolidones from LA was first reported using heterogeneous catalysis and dihydrogen as the reducing agent by Shilling¹² Crook¹³ and more recently by Manzer *et al.*¹⁴ Thus, Manzer *et al.* describe the need of different transition-metals such as Ni, Cu, Rh, Ru, Ir or Pt, grafted on silica, alumina or carbon as potential heterogeneous catalyst. 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*-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. E-factors¹⁵ comparison 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).

Table 1 Comparison of the E-factors from common procedures for the synthesis of 5-Methyl-N-Cyclohexylpyrrolidone.

Entry	Promoter	E-factor (kg waste/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 yield, 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

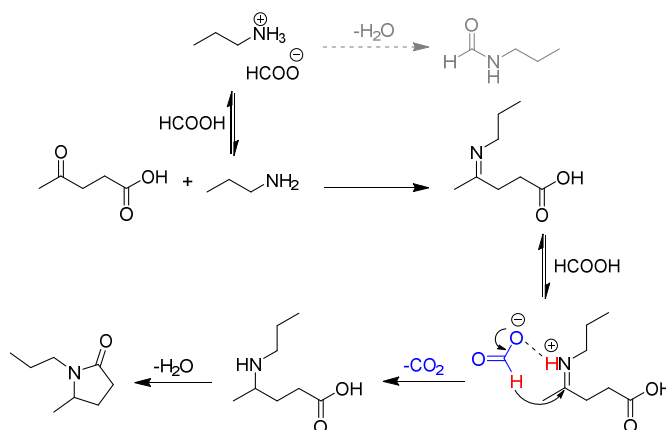
Within the frame of our efforts to develop an environmentally friendly, industrially applicable synthesis of the 5-Methyl-N-propylpyrrolidone (5Me-NPP) **2a**, we re-investigated the Ru-catalyzed approach by Huang *et al.*⁹ Aiming at developing an air and moisture tolerant catalyst, we considered first the combination of [Ru(*p*-cymene)Cl₂]₂ and (*o*-tolyl)₃P as a catalytic system for promoting the reductive amination of LA by N-propylamine in the presence of FA (Table 2).

Table 2 Effect of the catalyst loading

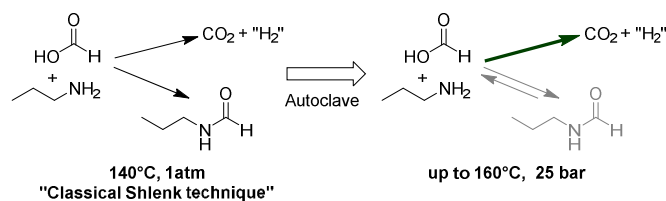
Entry	[Ru] mol%	Conversion (%) ^b	2a: 3a
1	1	86	1: 0
2	0.5	72	4: 1
3	0.05	58	6: 4
4	0	56	11: 9

^aRatio LA/FA/**1a** is 1:1:1. ^bDetermined by ¹H NMR

Interestingly, under Argon at normal pressure and in the absence of solvent, we discovered that decreasing strongly the catalyst loading did not influence drastically the outcomes of the reaction. Indeed, **2a** was still formed in decent amounts even in the presence of 0.05 mol% catalyst (Table 2, entries 1 to 3). More interestingly, when the reaction was carried out in the absence of catalyst¹⁷, **2a** was still obtained in 56% yield along with the formamide **3a** and H₂O (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

As depicted in scheme 1, formic acid is formally converted to CO₂ and "H₂" 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).

**Scheme 2** Limitation of the formamide formation under autogenous pressure

Indeed, in an isochoric system, the production of CO₂ and H₂ from the decomposition of FA allowed to produce the desired pyrrolidone **2a** as the only product. A maximum pressure of 25 bars after 4.5 h was obtained. Interestingly, a pressure monitoring can be used for determining the progress of the reaction assuming that CO₂ follow the ideal gas law (H₂ is consumed for the reduction of the imine function). Indeed the quantity of CO₂ released at full conversion corresponds to the theoretical pressure calculated from the decomposition of FA (Figure 1). As predicted, **2a** was obtained quantitatively in 4.2 hr at 25 bar for a temperature set at 160°C²⁰ (for details of calculations see supporting information). 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.

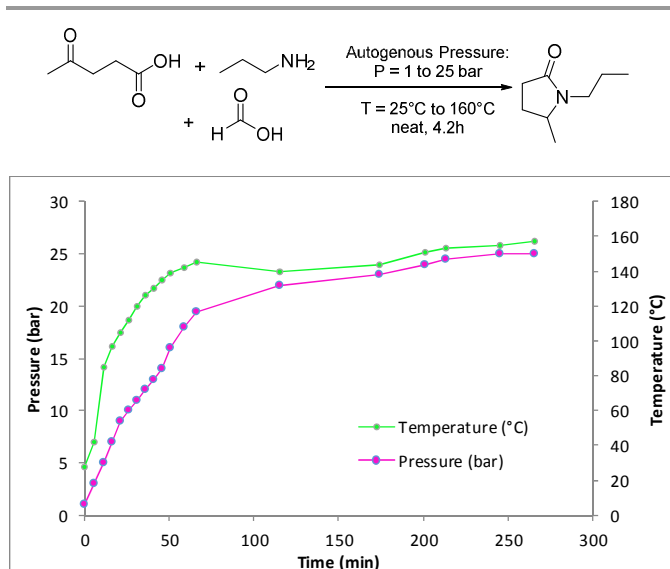


Fig. 1 Evolution of the temperature and self-generated pressure for the synthesis of **2a**. Ratio LA/FA/**1a** is 1:1:1. Maximal pressure of 25 bar corresponds to 100 % conversion of FA at 160°C.

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 supporting information).

Various N-substituted-5MeP were synthesised from LA, FA and several amines (Table 3). Preferentially, we chose aliphatic amines having a low boiling point and viscosity in order to obtain potential NMP alternatives for solvent applications

Table 3 Scope and limitation of the reaction

Entry	Amine R =	Conversion (%) ^a	Product	Yield (%) ^b
1	<i>n</i> -propyl (1a)	>99	5MeNPP (2a)	84
2	<i>n</i> -butyl (1b)	>99	5MeNBP (2b)	82
3	<i>i</i> -propyl (1c)	>99	5MeNiPP (2c)	80
4	<i>i</i> -butyl (1d)	>99	5MeNiBP (2d)	86
5	<i>t</i> -butyl (1e)	-	5MeNtBP (2e)	-
6	cyclohexyl (1f)	89	5MeNChP (2f)	88
7 ^c	<i>n</i> -octyl (1g)	86	5MeNOP (2g)	80
8 ^c	benzyl (1h)	>99	5MeNBzP (2h)	49

Conditions: 60 to 150 mmol scale, ratio LA/FA/**1a-h** : 1:1:1. ^aDetermined by ¹H NMR. ^bIsolated yield after distillation. ^cIsolated yield after extraction

Using our optimized conditions, aliphatic (iso)propyl- and (iso)butylamines **1a-d** reacted with full conversion (Table 3, entries 1 to 4). Resulting pyrrolidones **2a-d** were purified by distillation under reduced pressure and isolated in 80 to 86 % yield. The difference between conversion and yield is attributable to some loss during the distillation process that was realized on a laboratory scale (60 to 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 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, due to their higher boiling points, **2g** and **2h** were isolated by liquid-liquid extraction using EtOAc and a saturated NH₄Cl 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-Methylpyrrolidones 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.

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Notes and references

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† 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 run 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 Na₂CO₃, and extracted with AcOEt. The separated organic layer was washed with brine, and dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to afford the desired compounds. In the case of volatile amine (bp<100°C), a distillation under pressure was carried out and afforded a clear oil

Electronic Supplementary Information (ESI) available: Detailed synthetic procedure and spectral characterizations of the synthesized pyrrolidones. See DOI: 10.1039/c000000x/

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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 supporting information)
- 21 Reaction conditions for a maximum pressure of 64 bar: Total volume 100 mL, FA 1200 mmol, LA/FA/**1a**: **1:1:1**, Temperature 200°C (for details, see supporting information)

