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Catalyst-free transformation of levulinic acid into pyrrolidinones with formic acid†

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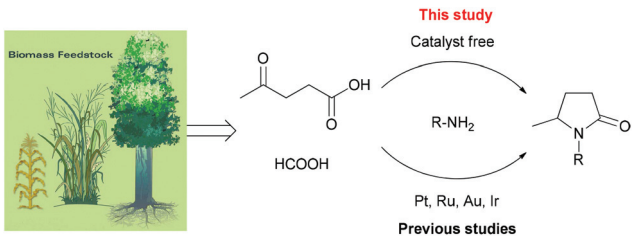
Levulinic acid (LA) is transformed into pyrrolidinones by formic acid in DMSO without a catalyst. Mechanistic studies suggest the involvement of an iminium intermediate and a rate-limiting hydride transfer step.

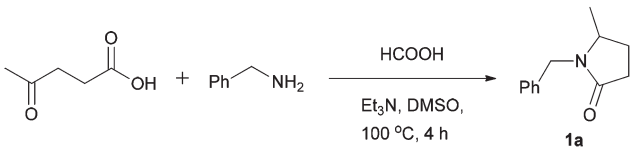
The use of renewable biomass to replace the limited and non-renewable fossil fuels has been recognised as an ideal solution for problems faced with fossil fuels.[1] Carbohydrates constitute the major part of biomass raw materials.[1c,2] LA is one of the platform chemicals derived from carbohydrates,[1p] and it can be transformed into fuels through γ-valerolactone (GVL).[3] Transforming LA into value added fine chemicals would also be desirable. One such example is the synthesis of pyrrolidinones from LA by reductive amination (RA). Heterogeneous catalytic hydrogenation was first explored for this reaction by Shilling,[4] Crook[5] and their co-workers, and later by Manzer,[6] Cao[7] and co-workers. Fu and co-workers reported the first homogeneous catalytic system for RA of LA to produce pyrrolidinones.[8] Recently, a mild and efficient iridium-catalysed RA of LA system was disclosed by our group.[9] In all the examples reported so far, however, precious metal based catalysts have to be used to effect this transformation. Herein, we present an example of RA of LA under catalyst-free conditions with formic acid as the reducing agent under mild conditions (Scheme 1).

Formic acid is a by-product formed during the acidic dehydration of carbohydrates into LA. It is also a common hydrogen source for transfer hydrogenation reactions.[1e] Reductive transformation of LA using formic acid as hydrogen source would be an ideal process, with the emitted carbon dioxide being reabsorbed by plants.[1u,3b–d,f,h,7–10] As indicated, catalysts were used in all of these systems. The use of formic acid for reduction reactions under catalyst-free conditions is rare, however. One famous example is the Leuckart–Wallach reaction discovered early in 1885.[11] The Leuckart reaction normally requires high temperature and has poor selectivity. Thus, the development of a mild and selective catalyst-free system for the RA of LA would be desirable.



Scheme 1 Catalyst-free transformation of LA into pyrrolidinones with formic acid.

During our effort to develop an iron-catalysed RA of LA with formic acid, we serendipitously discovered that LA could react with benzylamine to afford **1a** in DMSO in the presence of formic acid without a catalyst (Scheme 2). 72% conversion of LA into **1a** was obtained in DMSO in 4 h at 100 °C. The conversion of LA rose to 89% with the addition of one equivalent of triethylamine, which can balance the acidity of the system (ESI Fig. S1†). It is noteworthy that the temperature required for this conversion is much lower than the typical Leuckart reaction (mostly above 180 °C). Several solvents were then screened with 5 equivalents of formic acid and 1 equivalent of triethylamine at 100 °C for 4 h (ESI Table S1†). The results suggest



Scheme 2 Catalyst-free RA of LA. Reaction conditions: LA (1 mmol), benzylamine (2 mmol), HCOOH (5 mmol), Et_3N (1 mmol), DMSO (3 mL), 100 °C, 4 h, 89% conversion.

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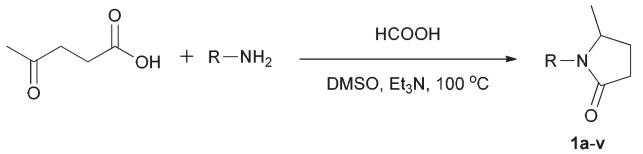
that the sulfinyl group is crucial for the reaction to proceed. In tetramethylene sulfoxide, 63% conversion was observed; however, all the other solvents, such as H_2O, MeOH, DCM, DMF, toluene, and CH_3CN, afforded less than 25% of conversion.

Various aliphatic amines were then reacted with LA to test the generality of this protocol. The results are summarised in Table 1.

Good to excellent isolated yields were obtained for benzylic amines with differing substituents on the phenyl ring (Table 1, entries 1–11). Activities were lower for 4-CF_3, 3-F, and 3,4-Cl substituted substrates (Table 1, entries 6, 8, 11). The non-benzylic amine, phenylethylamine, also reacted well (Table 1, entry 12). Varying the chain length of the aliphatic amines did not affect the activities very much (Table 1, entries 13–17). Branched aliphatic amines afforded similar yields (Table 1, entries 18–20). A cyclic amine also worked well (Table 1, entry 21). Good yield was given by a chiral amine, albeit with a low diastereoisomeric ratio (Table 1, entry 22).

The success enjoyed by aliphatic amines could not be shared with aromatic amines, however. Only 50% conversion was obtained when using *p*-anisidine at the above optimal conditions. By increasing the amount of amine to 3 equivalents and adding *p*-anisidine and formic acid through 4 portions, the conversion of LA could rise to 79% and a 70% isolated yield of the product was obtained. However, acceptable yields were only obtained for electron-rich aromatic amines (Table 2, entries 1–5). Other aromatic amines tested including aniline and 3-methoxylaniline all failed to give more than 50% yield.

Table 1 RA of LA with aliphatic amines[a]

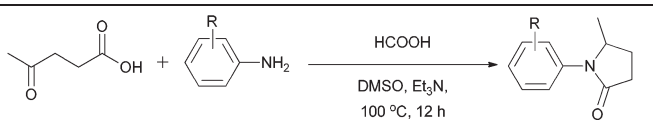


1a-v

Entry	R	Product	Time (h)	Yield[b] (%)
1	Benzyl	**1a**	12	87
2	4-OMe-benzyl	**1b**	12	89
3	4-Me-benzyl	**1c**	12	91
4	4-F-benzyl	**1d**	12	89
5	4-Cl-benzyl	**1e**	12	88
6	4-CF_3-benzyl	**1f**	15	76
7	3-OMe-benzyl	**1g**	12	89
8	3-F-benzyl	**1h**	12	74
9	2-OMe-benzyl	**1i**	12	91
10	2-F-benzyl	**1j**	12	81
11	3,4-Cl-benzyl	**1k**	12	72
12	1-Phenylethyl	**1l**	12	86
13	1-Butyl	**1m**	12	86
14	1-Pentyl	**1n**	12	90
15	1-Hexyl	**1o**	12	93
16	1-Octyl	**1p**	12	93
17	1-Dodecyl	**1q**	12	88
18	Isopentyl	**1r**	15	77
19	3-Pentyl	**1s**	15	87
20	2-Ethylhexyl	**1t**	12	91
21	Cyclohexyl	**1u**	12	85
22	(*R*)-1-Phenylethyl	**1v**	12	88 (1.5 : 1)[c]

[a] Reaction conditions: LA (1 mmol), amine (2 mmol), HCOOH (5 mmol), Et_3N (1 mmol), DMSO (3 mL), 100 °C. [b] Isolated yield. [c] Numbers in brackets refers to dr.

Table 2 RA of LA with aromatic amines[a]



2a-k

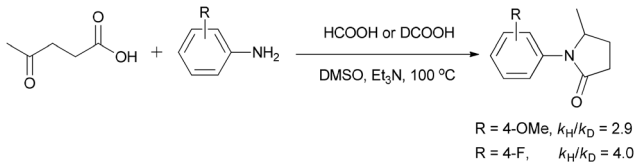
Entry	R	Product	Yield[b] (%)
1	4-OMe	**2a**	70
2	4-Me	**2b**	44
3	3,4-Me	**2c**	75
4	3,4-OMe	**2d**	71
5	4-NH_2	**2f**	55
6	3-OMe	**2e**	26
7	4-H	**2g**	34
8	4-F	**2h**	28
9	4-Cl	**2i**	13
10	4-Br	**2j**	8
11	4-OCF_3	**2k**	23

[a] Reaction conditions: LA (1 mmol), amine (3 mmol), HCOOH (5 mmol), Et_3N (1 mmol), DMSO (3 mL), 100 °C. [b] Isolated yield.

In our previous study of the same reaction using an iridium catalyst, evidence points to the reaction proceeding *via* the hydrogenation of an *in situ* formed iminium ion followed by spontaneous cyclisation.[9] A similar pathway appears to be operating for the transformation in question, except with the reducing hydride coming from the formate instead of a metal complex. Thus, when LA was reacted with benzylamine in the presence of DCOOH, the ^{1}H NMR of the isolated product showed that the deuterium atom exclusively goes to the C5 carbon, supporting the involvement of an iminium intermediate (ESI Scheme S1†). In previous studies, a number of reducible intermediates were suggested for the Leuckart reaction, including in particular imines and enamines.[11c,12] The reaction shown in Scheme S1† rules out the possibility of an enamine intermediate.

In order to gain further insight into the reaction mechanism, we studied the kinetic isotope effect by measuring the initial rates of the reaction of LA with *p*-anisidine and 4-F-aniline using HCOOH and DCOOH. We observed k_H/k_D = 2.9 for *p*-asinidine and 4.0 for 4-F-aniline, respectively, which suggest that the transfer of hydride from formic acid to the imine or iminium intermediate is involved in the rate-limiting step (Scheme 3).[13]

The kinetic isotope data appear at odds with the results in Table 2, however. In fact, a "Hammett plot" for different substituents *para* to the amino group of aromatic amines based on the yields reveals a surprisingly linear relationship, with ρ being −1.4 (Fig. 1),[14] suggesting a positive charge, rather than a negative one, being developed at the transition state of the rate limiting step, which is inconsistent with hydride transfer being involved. One explanation for these somehow conflicting results is the rate-limiting hydride transfer step being preceded



Scheme 3 Kinetic isotope effect experiments for RA of LA. The reactions were carried out in NMR tubes and the initial rates (based on <10% conversions) were measured by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

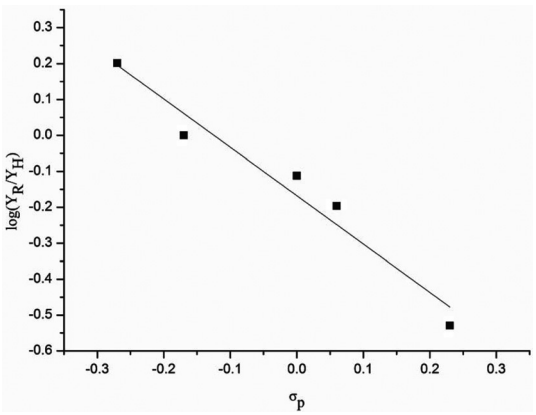
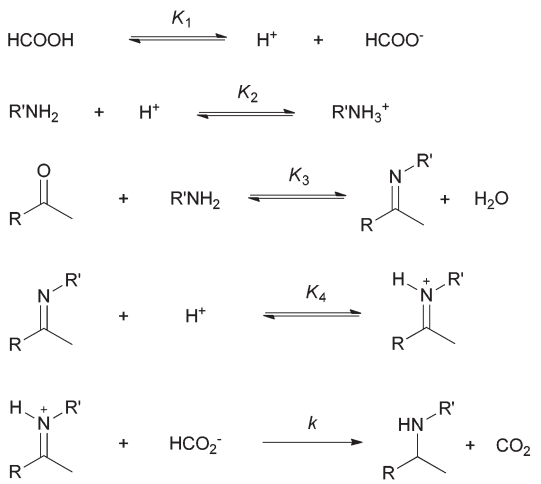


Fig. 1 "Hammett plot" for substituents *para* to the amino group of aromatic amines based on yields in 12 h.

by some complex equilibria as illustrated in Scheme 4. The kinetic isotope effect mainly results from the rate difference caused by using HCOOH *vs.* DCOOH in the hydride transfer step defined by the rate constant k, whilst the "Hammett plot" is to some degree a reflection of the overall rate constant k_{obs}, which is likely to be a compound of k and the equilibrium constants K_1–K_4. Although k is expected to increase with electron-deficient amines, the equilibrium constants $K_3 \times K_4$ may become larger with more electro-rich ones. The increase in $K_3 \times K_4$ could render k_{obs} larger with amines bearing more electron-donating substituents, leading to a negative ρ.



Scheme 4 Possible equilibria preceding the hydride transfer step, which are likely to complicate the electronic effects of amines on the overall reaction rate.

The reason why DMSO is so effective a solvent is unclear. One possible explanation is found in its high solvent basicity (0.647 *vs.* 0.613 for DMF, 0.286 for CH_3CN, 0.128 for toluene and 0.025 for water),[15] which would be expected to promote the nucleophilic attack by the amine at the ketone and by the formate at the iminium ion. Another possible explanation is from the abnormal behaviour of pK_a values of RNH_3^+. The pK_a of a substance normally increases, when switching the solvent from water to DMSO. However, this is not the case for RNH_3^+.[16a] RNH_3^+ has smaller or similar pK_a values in DMSO than in water. For example, $PhNH_3^+$ has a pK_a of 4.6 in water and 3.6 in DMSO and Et_3NH^+ has a pK_a of 10.8 in water and 9.0 in DMSO.[16] For formic acid, its pK_a in water is 3.77 and it is expected to increase in DMSO, as judged by that of acetic acid, whose pK_a increases from 4.76 to 12.6 on going from water to DMSO.[16] Thus the pK_a of aromatic or aliphatic amine salts could be similar or smaller than that of formic acid in DMSO, ensuring that a large amount of free amines are present in DMSO to participate in the imine formation step.

In conclusion, a catalyst-free system for RA of LA has been developed. The solvent DMSO is critical for the high reactivity observed. Mechanistic studies suggest that the rate-limiting step for the reaction is hydride transfer from formic acid to the iminium intermediate. The method described here is an extension of the classic Leuckart–Wallach reaction and provides a practical, alternative way to convert LA to value-added chemicals.

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