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PII: S0040-4039(16)30019-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.01.018
Reference: TETL 47182

To appear in: *Tetrahedron Letters*

Received Date: 1 December 2015
Revised Date: 28 December 2015
Accepted Date: 6 January 2016

Please cite this article as: Ortiz-Cervantes, C., Flores-Alamo, M., García, J.J., Synthesis of Pyrrolidones and Quinolines from the Known Biomass Feedstock Levulinic Acid and Amines, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.018

Synthesis of Pyrrolidones and Quinolines from the Known Biomass Feedstock Levulinic Acid and Amines

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Abstract

The catalytic conversion of biomass-derived compounds into value-added products such as food additives, agrochemical components and pharmaceutical formulations, is a promising and cost effective synthetic strategy. Here, we describe the synthesis of a variety of *N*-(alkyl, aryl)-5-methyl-2-pyrrolidones through the reductive amination of levulinic acid using formic acid as the hydrogen source. This system is catalyzed by 3.8 nm ruthenium nanoparticles that were prepared by thermal decomposition of $[Ru_3(CO)_{12}]$ in solvent-free conditions. When the reactions were carried out without the catalyst, the pyrrolidones were obtained with low yield and poor selectivity. In addition, the reaction between levulinic acid and 2-ethynylaniline produced 2-(2,4-dimethylquinolin-3-yl) acetic acid (**8**) in mild and metal-free conditions with good yield. Furthermore, the synthesis of substituted quinolines was achieved through a condensation reaction between levulinic acid and different 2-alkynylanilines promoted by *p*-toluenesulfonic acid, this method is highlighted as a novel procedure for preparation of quinolines.

Keywords: amines; cyclization, heterocycles, levulinic acid; quinolines; reductive amination; ruthenium nanoparticles.

Introduction

Pyrrolidones such as 5-methyl-*N*-(methyl, aryl, or cyclohexyl)-2-pyrrolidones are value-added products that have been widely used as solvents, surfactants, chelating agents, agrochemical components, transdermal patches or pharmaceutical formulations.[1]

The transformation of oxo-carboxylic acid compounds to pyrrolidones by reductive amination with ammonia was for the first time in the 1960s by Shilling.[2] Then, in several patents, Manzer described the reductive amination of levulinic acid (LA) under high hydrogen pressure via heterogeneous catalysts.[3] Very recently, Shimizu and co-workers reported the reductive amination of LA with H_2 catalysis supported by Pt catalysts under solvent-free conditions.[4]

Of the variety of biomass-derived feedstocks, levulinic acid is potential chemical platform with a broad range of applications.[5] Formic acid (FA)[6] and levulinic acid[7] can be obtained from biomass compounds such as cellulose, and FA is an efficient and reversible storage material for hydrogen under very mild reaction conditions in the presence of the suitable catalysts.[8] Moreover, FA has been used for the reductive amination of LA as an alternative to hydrogen pressure with Au heterogeneous catalysts;[9] several ruthenium sources with phosphine ligands as catalysts have been tested in the production of pyrrolidones from LA with FA. Including the use of $[Ru(p\text{-cymene})Cl_2]_2$ with $P^tBu{\cdot}HBF_4$ offers a high yield but limited scope.[10]

Recently, Wang and co-workers reported the use of iridium catalysts in transfer hydrogenation to produce pyrrolidones by reductive amination of LA with an excess of FA.[11] The same group also reported metal-free synthesis of pyrrolidones in DMSO but with a stoichiometric amount of NEt_3.[12] In addition, Andrioletti and co-workers reported another

example of metal-free reductive amination of LA; however, the reaction required more forceful conditions including higher temperatures (160 – 200 °C).[13]

On the other hand, quinolines are an important heterocyclic compound due to their antibacterial,[14] anthelmintic[15] and anti-inflammatory properties.[16] There is a vast literature on quinoline-derived compound syntheses. Several syntheses are based on the Friedländer strategy with 2-aminobenzaldehyde and acetaldehyde[17] as well as the reaction among various anilines including those with β-keto esters,[18] alkynes,[19] ethyl vinyl ether,[20] α,β-unsaturated carbonyl compounds[21] have been reported.[22]

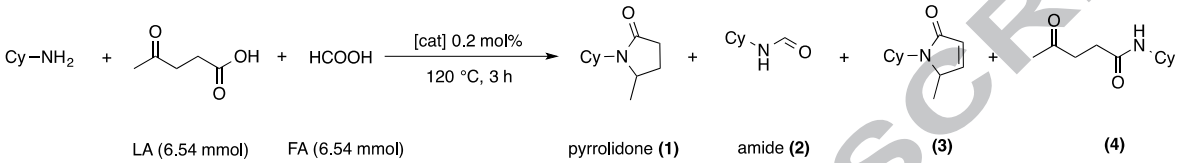
In this work, we disclose the preparation of pyrrolidones by reductive amination using the formic acid dehydrogenation catalyzed with Ru-NPs to obtain a variety of 5-methyl-*N*-(aryl, alkyl)-2-pyrrolidones under solventless conditions in high yields. In addition, the first metal-free synthesis of quinoline-derived compounds such as 2-(2,4-dimethylquinolin-3-yl) acetic acid (**8)** from a reaction between biomass-derived levulinic acid and alkynylanilines is described.

Results and discussion

Reductive amination of LA was performed with cyclohexylamine and FA. The latter was the hydrogen source and key results are summarized in **Table 1**. In addition to the results shown at **Tables 1** and **3** a wide variety of reaction conditions can be found in SI. Then we selected the milder reaction conditions, shorter reaction times and better yields. In the absence of catalyst (**Table 1**, entry 1), product **1a** was obtained as a mixture but in the presence of nanoparticle precursor [$Ru_3(CO)_{12}$], there was an increase in pyrrolidone yield. Other pre-catalysts or catalyst precursors such as [(dtbpe)$PdCl_2$] (dtbpe = 1,2-(bis-di-*tert*-

butylphosphino)ethane) and $[H_4Ru_4(CO)_{12}]$ were used and showed lower activity. The main role of the corresponding catalyst is believed to involve formic acid decomposition to produce hydrogen.

Table 1. Reductive amination of levulinic acid with formic acid and cyclohexylamine.



Entry	[cat]	Conv. (%)	1 (%)[a]	2 (%)[a]	3 (%)[a]	4 (%)[a]
1	-----	100	67	18	10	5
2	$[Ru_3(CO)_{12}]$	100	94	2	1	3
3 [b]	$[Ru_3(CO)_{12}]$	100	97	2	1	-
4	$[H_4Ru_4(CO)_{12}]$	100	81	11	3	5
5	$[(dtbpe)PdCl_2]$	93	72	8	6	7

[a] All yields (mole%) were determined by GC-MS. [b] Hg drop test (0.07 mmol).

The formation of Ru-NPs from thermal decomposition of $[Ru_3(CO)_{12}]$ in solvent-free conditions was shown via TEM micrographs (**Figure 1**). The Ru-NPs with a mean diameter of *ca.* 3.8 nm catalyzed the formic acid decomposition. Previously, we reported the formic acid decomposition to levulinic acid hydrogenation catalyzed by Ru-NPs.[23]

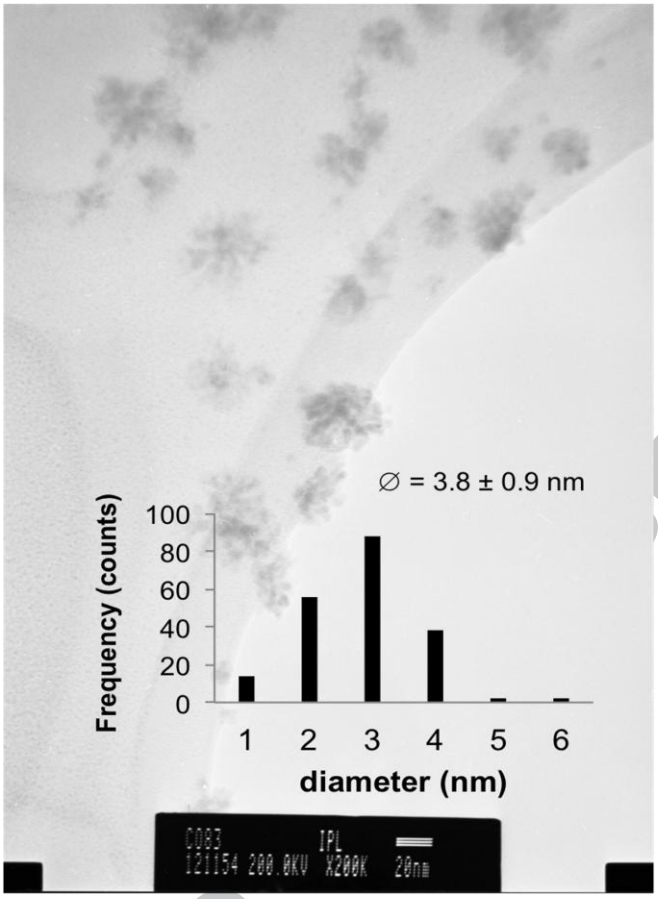
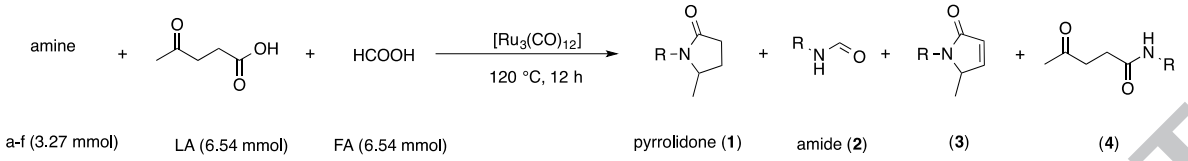
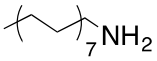
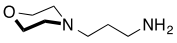
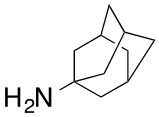


Figure 1. TEM image (20 nm scale) of Ru-NPs from thermal decomposition of $[Ru_3(CO)_{12}]$ under solvent-free conditions.

In general, products from reductive amination of LA with alkyl amines were obtained by FA decomposition catalyzed by Ru-NPs in high yields (**Table 2**). Of note, amines with bulky substituents did not favor pyrrolidone formation due to steric hindrance. This does not allow nucleophile attack of the amine over the LA (entries 4 and 6).

Table 2. Reductive amination of levulinic acid with aliphatic amines

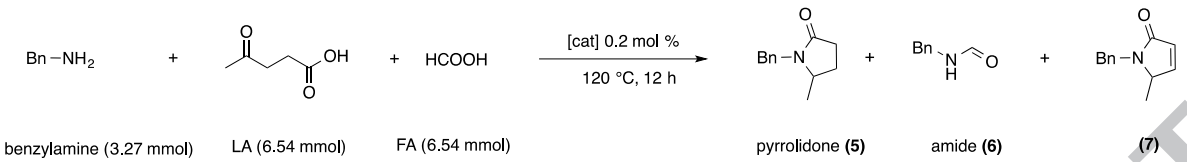


Entry	amine (a-f)	Conv. (%)[a]	1 (%)[a]	2 (%)[a]	3 (%)[a]	4 (%)[a]
1		100	97	1	2	-
2		100	97	3	-	-
3		100	88	12	-	-
4	*t*-Bu-NH_2	100	38	-	-	61
5	*s*-Bu-NH_2	100	90	-	-	10
6		83	33	-	12	38

With 0.2 mol% of nanoparticles precursor ($[Ru_3(CO)_{12}]$) [a] All yields (mole%) were determined by GC-MS.

In both **Tables 1** and **3**, entry 1, the control experiments indicates that low yields were obtained without the use of Ru-NPs (67% vs 43% respectively), in both cases the yield was increased with the use of Ru-Nps (**Tables 1** and **3**, entry 2). However, the production of pyrrolidone from cyclohexylamine (**Table 1**, entry 3) did not decrease during mercury drop test *vs*. a 20% decrease in the benzyl pyrrolidone synthesis (**Table 3,** entry 3). Therefore, we conclude that the *N*-cyclohexyl-5-methyl-2-pyrrolidone production is faster and affected by mercury drop. On the other hand, a yield decrease in the reaction with benzylamine confirms the formation of Ru-NPs inactivated by mercury.[24]

Table 3. Reductive amination of levulinic acid with FA and benzylamine.



benzylamine (3.27 mmol) LA (6.54 mmol) FA (6.54 mmol) pyrrolidone **(5)** amide **(6)** **(7)**

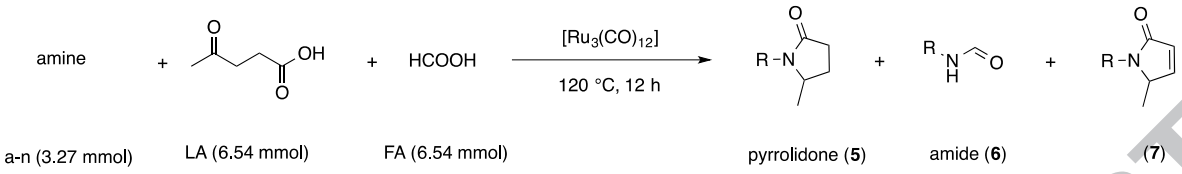
Entry	[cat]	Conv. (%)[a]	5 (%)[a]	6 (%)[a]	7 (%)[a]
1	-----	100	43	41	16
2	$[Ru_3(CO)_{12}]$	100	93	3	4
3	$[Ru_3(CO)_{12}]^b$	100	73	5	22

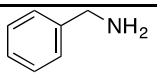
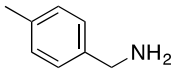
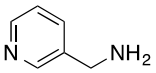
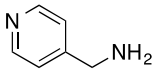
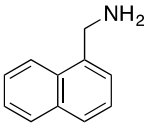
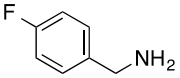
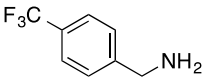
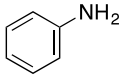
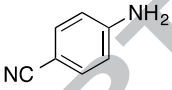
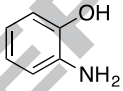
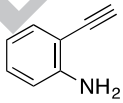
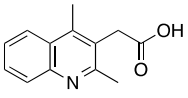
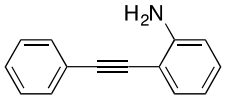
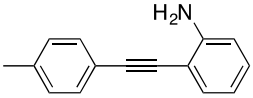
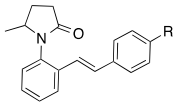
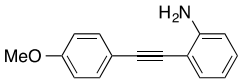
[a] All yields (mole%) were determined by GC-MS. [b] Hg drop test (0.07 mmol).

The reductive amination of LA was carried out using a variety of aromatic amines (**Table 4**) to produce the respective pyrrolidones. Regarding the electronic and steric properties of amines, higher conversions were obtained with electron-donor substituents (entry 2) as in the case of methyl group. The electron withdrawing groups such as CF_3 substituent (entry 7) did not favor the reaction. In the case of amines with pyridine groups, position 4 is more electron deficient than that in position 3. Thus, the latter showed a higher selectivity to the pyrrolidone product.

Surprisingly, when 2-ethynylaniline was used, the main product was 2-(2,4-dimethyl-quinolin-3-yl) acetic acid (**8**). This is a condensation product of LA and 2-ethynylaniline. In light of this result, the same reaction conditions were assessed for a variety of alkynylanilines (entries 12 – 14, **Table 4**). However, these amines were not soluble in the reaction mixture and have a melting point over 130 ºC—thus, their reactivity was low. Of note, the use of solvents such as THF, mesitylene and xylene resulted in very low conversions. When alkynylanilines were used there was a poor pyrrolidone formation as well as a reduction in the alkyne to *trans*-alkene transformation.

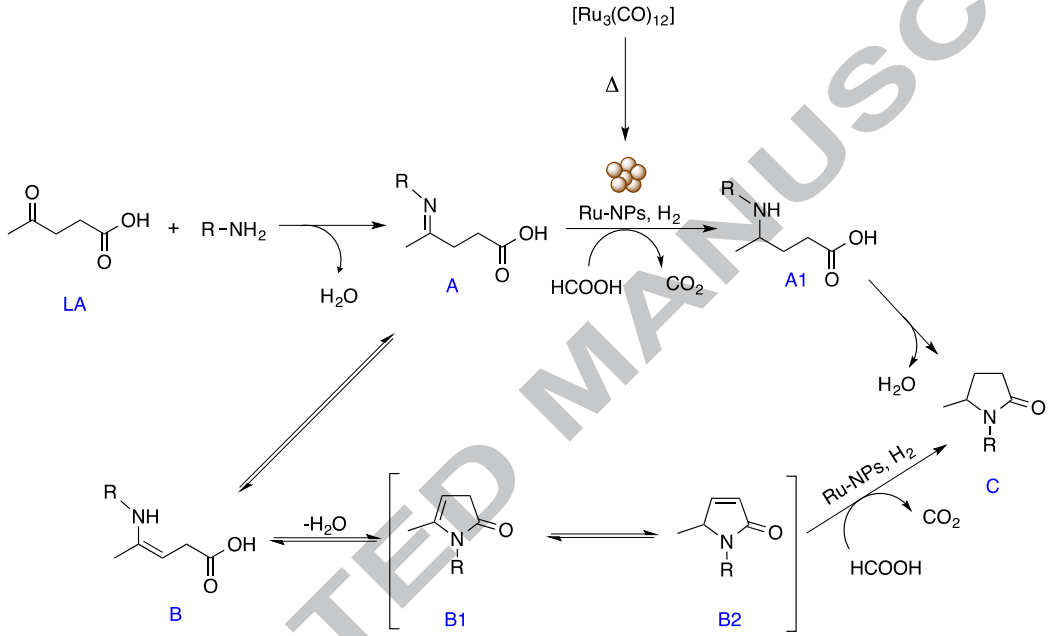
Table 4. Reductive amination of levulinic acid with aromatic amines



Entry	amine (a-n)	Conv. (%)[a]	5 (%)[a]	6 (%)[a]	7 (%)[a]
1		100	93	3	4
2		100	95	5	-
3		100	76	18	6
4		100	65	31	4
5		100	91	8	1
6		100	77	21	2
7		100	48	44	8
8		100	89	1	10
9		88	50	40	-
10		89	66	22	-
11		100		53(**8**)	-
12[b]		70	40	-	-
13[b]		46	 35	-	-
14[b]		30	11	-	-

Using 0.2 mol% of nanoparticles precursor ($[Ru_3(CO)_{12}]$) [a]All yields (mole%) were determined by GC-MS. [b] *trans*-alkene pyrrolidone, R = H, Me, OMe.

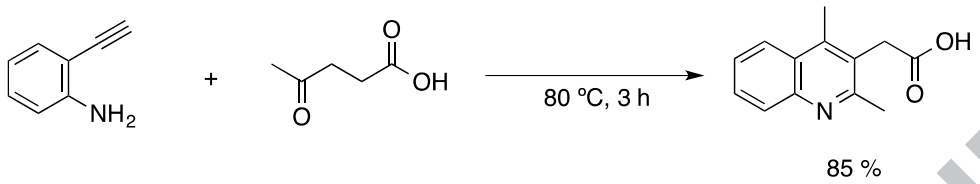
A mechanistic proposal for the reductive amination of LA is depicted in **Scheme 1**. First, imine **A** forms from LA and the amine, and then the imine-enamine reaches equilibrium with the concomitant dehydration process that produces equilibrium species **B1** and **B2.** The formic acid decomposition via ruthenium nanoparticles then generates hydrogen and carbon dioxide. Finally, the hydrogenation of compound **B** produces the corresponding pyrrolidone.



Scheme 1. Mechanistic proposal for reductive amination of LA.

A series of reaction conditions were explored to improve the yield of compound **8**. Compound **8** was prepared under metal-free conditions as depicted in **Scheme 2**. Initially, the formation of compound **8** begins with the hydration of alkyne to the corresponding ketone that produces the respective imine through condensation with LA. This finally leads to the formation of the quinoline **8** as shown in **Scheme 3** *vide infra*. Suitable crystals for

X-ray determination of **8** were obtained by slow evaporation of THF. **Figure 2** displays the corresponding ORTEP drawing.



Scheme 2. Condensation reaction of levulinic acid and 2-ethynylaniline.

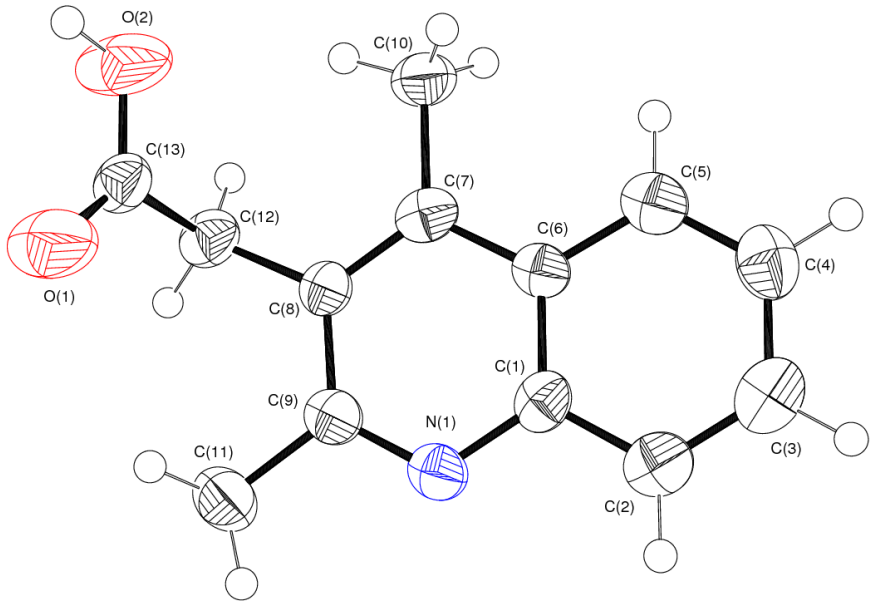
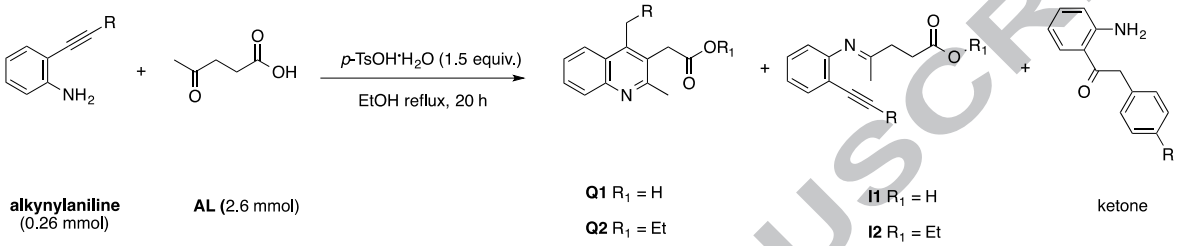


Figure 2. ORTEP diagram for compound **8**. The thermal ellipsoids are drawn at 50% probability. Selected distances (Å) and angles (°): C(1) – N(1) = 1.361(4), C(7) – C(8) = 1.379(4), C(7) – C(10) = 1.512(4), C(8) – C(9) = 1.422(4), C(8) – C(12) = 1.513(4), C(9) – N(1) = 1.324(4), C(9) – C(11) = 1.501(4), C(12) – C(13) = 1.502(4), C(13) – O(1) = 1.203(4), C(13) – O(2) = 1.267(4); C(8) – C(7) – C(10) = 122.6(3); C(13) – C(12) – C(8) = 112.8(3); O(1) – C(13) – O(2) = 122.8(3); and C(9) – N(1) – C(1) = 119.9(3).

On the other hand, quinoline-derived compounds were synthetized using LA and 2-alkynylanilines with a modest conversion using a previously reported methodology for 4-alkyl-2,3-disubstitued quinolines promoted by *p*-toluenesulfonic acid.[18] As shown in **Table 5,** the main product from the condensation reaction between LA and alkynylanilines was

the quinoline-derived compound as well as the ketone compound derived from the alkyne hydration.

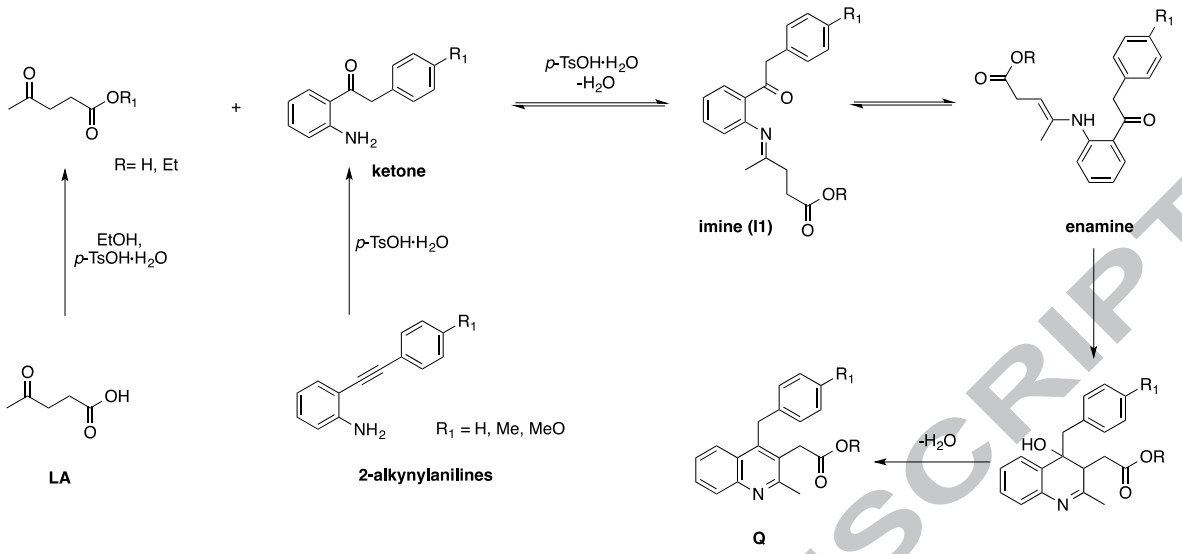
Table 5. Synthesis of quinoline-derived compounds from levulinic acid and 2-alkynylanilines



Entry	R	Conv. (%)[a]	Q1 (%)[a]	Q2 (%)[a]	ketone (%)[a]	I1 (%)[a]	I2 (%)[a]	others (%)[a]
1	H	89	48	7	3	18	1	12
2	Me	77	38	6	3	16	2	12
3	OMe	37	12	9	0	5	3	8

[a] All yields (mole %) were determined by GC-MS.

A possible route to quinoline formation is presented in **Scheme 3**. First, the ketone is produced by a hydration reaction promoted by the Brønsted acid *p*-TsOH.[25] The condensation then leads to the enamine equilibrium to produce the imine. Finally, the cyclization product forms and its dehydrative aromatization to results in a quinoline derivative.



Scheme 3. A possible route to the synthesis of quinoline-derived compounds

Conclusions

The catalytic conversion of biomass-derived levulinic acid into valuable pyrrolidones was achieved via reductive amination with formic acid-produced hydrogen and catalyzed via ruthenium nanoparticles. In addition, quinoline-derived compounds were prepared by a novel method under metal-free conditions promoted by *p*-toluenesulfonic acid from the condensation reaction between levulinic acid and alkynylanilines in good yields. The quinoline compound from 2-ethynylaniline and LA produced 2-(2,4-dimethylquinolin-3-yl) acetic acid selectively under mild, metal-free and solventless conditions.

ASSOCIATED CONTENT

- **Supporting Information available.** Includes experiments and relevant NMR spectra, GC-MS determinations and Crystal data for **8**.

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Acknowledgements

We thank CONACYT (178265) and DGAPA-UNAM (IN-202516) for their financial support. C. O-C also thanks CONACYT for a graduate studies grant. We thank Iván Puente-Lee (USAI-UNAM) for TEM studies and Dr. Alma Arévalo for technical support.

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Graphical Abstract

Synthesis of Pyrrolidones and Quinolines from the Known Biomass Feedstock Levulinic Acid and Amines

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