chemistry proceedings

MDPI

*Proceedings Paper*

# Synthesis of 2-Aminopyridine Lactones and Studies of Their Antioxidant, Antibacterial and Antifungal Properties †

**Fadila Salhi [1,3], Nawel Cheikh [2,3], Didier Villemin,[1,*] and Nathalie Bar [1]**

[1] Normandie Université France, ENSICAEN, LCMT, UMR CNRS 6507, INC3 M, FR 3038, Labex EMC3, LabexSynOrg, 6 Bd Maréchal Juin, 14050 Caen, France
[2] Laboratoire de Catalyse et Synthèse en Chimie Organique, Faculté des Sciences, Université Abou-Bakr Belkaid, BP 119, Tlemcen 13000, Algeria
* Correspondence: didier.villemin@ensicaen.fr; Tel.: +33-231-452-840)
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15 November 2021–30 November 2020. Available online: https://ecsoc-25.sciforum.net/.

**Abstract:** In the present work, the synthesis and biological activities of substituted 2-aminopyridine δ-lactone derivatives were achieved. 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile was synthesised from 4-hydroxy-4-methylpentan-2-one, followed by its transformation in enaminonitrile with DMFDMA. The antioxidant effects of substituted 2-aminopyridine δ-lactone derivatives were evaluated through DPPH assay and revealed a great antioxidant capacity. The antifungal and antibacterial activities were investigated by disc diffusion method against clinical Gram-negative bacteria and against clinical fungi. The study shows moderate to very good antibacterial and antifungal activities for the new substituted 2-aminopyridine δ-lactone derivatives.

**Keywords:** 2-aminopyridines; bis-2-aminopyridines; antioxidant; DPPH; radical scavenger; antibacterial activity; antifungical activity

**Citation:** Salhi, F.; Cheikh, N.; Villemin, D.; Bar, N. Synthesis of 2-Aminopyridine Lactones and Studies of Their Antioxidant, Antibacterial and Antifungal Properties. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Julio A. Seijas

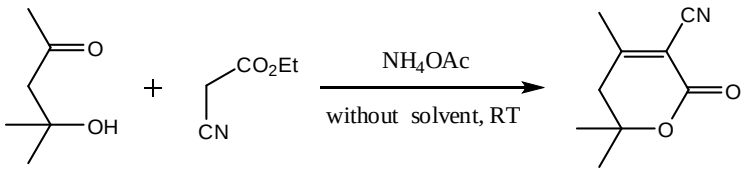
Published: 15 November 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Copyright:** © 2021 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

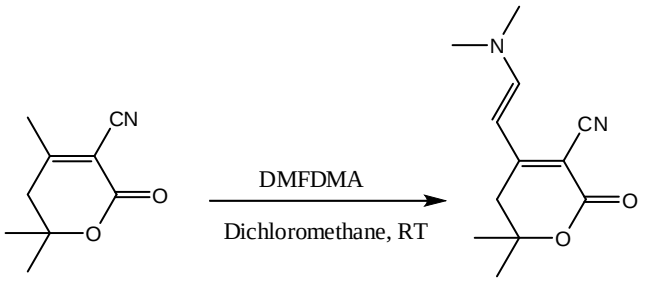
## 1. Introduction

Substituted 2-aminopyridine δ-lactone derivatives were achieved. 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile was synthesised from 4-hydroxy-4-methylpentan-2-one[], followed by its transformation in enaminonitrile with DMFDMA[].



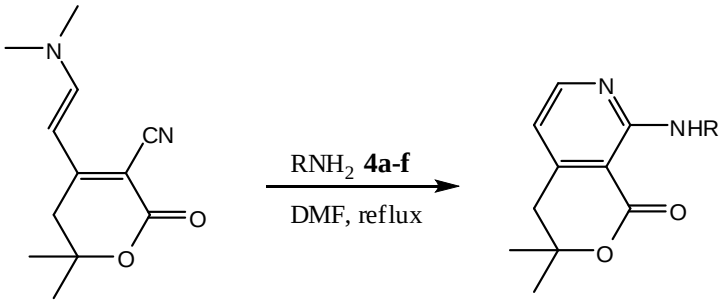

**2** **1**

The compound **3** was prepared by the reaction of δ-lactone nitrile «4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile » **1** with dimethylformamide dimethylacetal DMFDMA in stoichiometric amounts. The reaction was performed at room temperature during 24 h and afforded good overall yield (72%) [1].



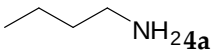
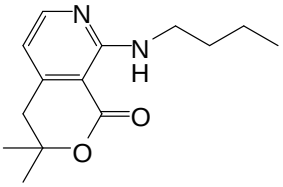
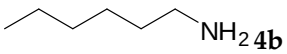
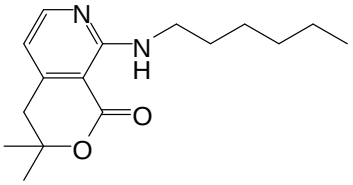
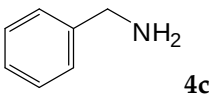
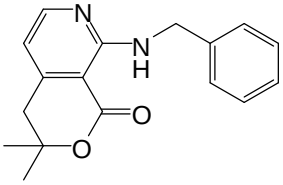
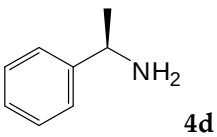
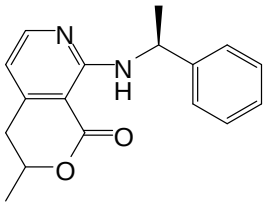

**1** **3**

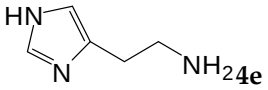
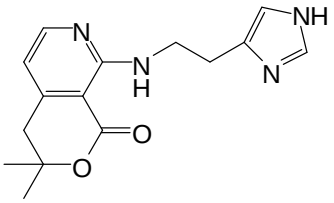
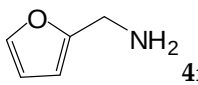
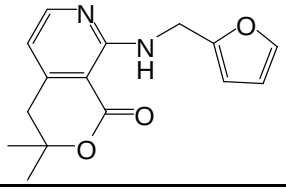
The reaction of enaminolactone nitrile **3** and primary amines **4a–f** in refluxed DMF according to our previous work [1] results in new substituted 2-aminopyridines **5a–f.**




**3** **5a-f**

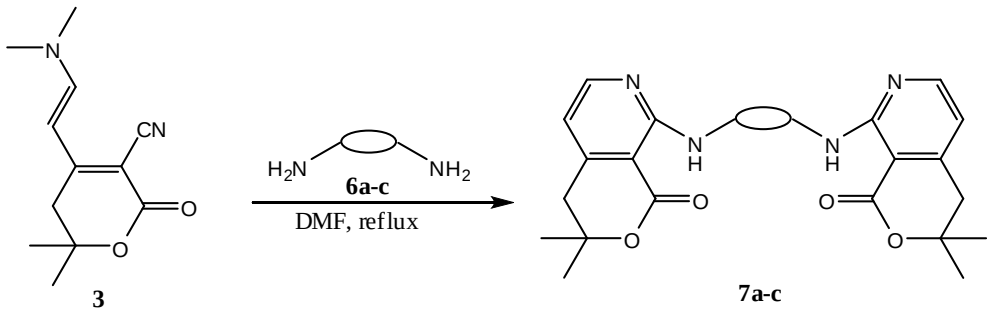
**Table 1.** Synthesis of 2-aminopyridine lactones.

| Entry | Enaminolactone | $RNH_2$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **3** |  **4a** |  **5a** | 95 |
| 2 | **3** |  **4b** |  **5b** | 87 |
| 3 | **3** |  **4c** |  **5c** | 92 |
| 4 | **3** |  **4d** |  **5d** | 96 |

| | | | | |
|---|---|---|---|---|
| 5 | **3** |  **4e** |  **5e** | 95 |
| 6 | **3** |  **4f** |  **5f** | 96 |

The structure of substituted 2-aminopyridine δ-lactones characterised by spectroscopic methods (IR, $^{1}$H NMR, $^{13}$C NMR and MS).

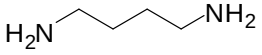
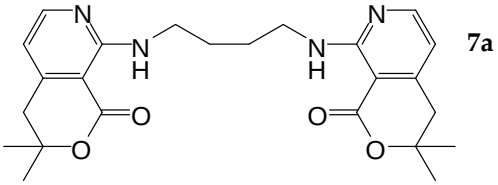
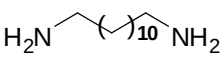
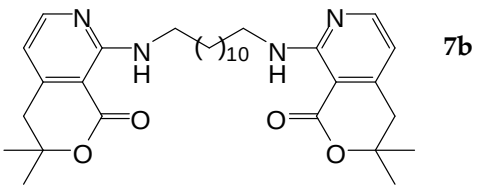
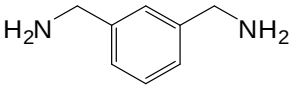
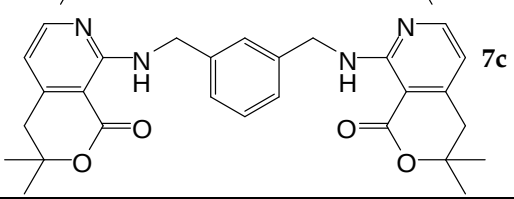
The reactions between 1 equiv of diamines **6a–c** with 2 equiv of enaminolactone nitrile **3**. The mixture was refluxed in DMF during 6h. After removing of the solvent and purification by column chromatography, we afforded the new original bis-(2-aminopyridines) **7a–c** in moderate to good yields (Table 2)




**3** **7a-c**

The structure of the compounds **7a-c** was confirmed by spectral data (IR, $^{1}$H NMR and $^{13}$CNMR).

**Table 2.** Synthesis of bis-2-aminopyridine lactones.

| Entry | | $RNH_2$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **3** |  **6a** |  **7a** | 57 |
| 2 | **3** |  **6b** |  **7b** | 60 |
| 3 | **3** |  **6c** |  **7c** | 89 |

## 2. Antioxidant Effects

The antioxidant effects of substituted 2-aminopyridine δ-lactone derivatives were evaluated through DPPH assay and revealed a great antioxidant capacity.

For initial screening of antioxidant activity DPPH on TLC was employed. [2] After the qualitative confirmation of antioxidant potential, spectroscopic measurements were made through DPPH assay. The antioxidant proprieties were measured and evidenced in terms of their efficient concentration $IC_{50}$, as well as their reduction kinetics. [3] Evaluation of the antioxydant activity by the test of DPPH, revealed a great antioxydant capacity for the most of compounds tested with a variation of $IC_{50}$ between 1.30–3.61 mg/mL and times of reaction of 30 min.

## 3. Antifungal and Antibacterial Activities

The antifungal and antibacterial activities of 2-aminopyridines and bis-2-aminopyridines were investigated in vitro in order to evaluate their efficacy. The antibacterial activity of the compounds was determined by the disc diffusion method [4,5] against clinical Gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria: *Staphylococcus aureus, Listeria monocytogenes* and *Bacillus cereus*. The antifungal activity of the compounds was determined by using a direct-contact and agar diffusion test [6] against clinical fungi *Aspergillus flavus* and *Aspergillus ochraceus.* The compounds showed moderate to very good antibacterial and antifungal activities, that the **5b**, **5d**, **5e** and **5f** presents a best minimal inhibitory concentration (MIC) with 62.5 μg/mL. The *Aspergillus ochraceus* strain revealed a stronger sensitivity than *Aspergillus flavus* to all compounds tested, While that the **7c** and 7**b** showed a braod-spectrum antifungal activity again pathogenic *Aspergillus ochraceus* with an inhibition percentage of 77% and 78%, respectively. Based our results, the compounds of 2-aminopyridines and bis-2-aminopyridines can be considered as a source of novel antibiotic and antifungal.

**Experimental:** described in supplementary informations.

## 4. Conclusions

The study shows moderate to very good antibacterial and antifungal activities for the new substituted 2-aminopyridine δ-lactone derivatives.

## References

1. Salhi, F.; Cheikh, N.; Villemin, D.; Mostefa-Kara, B.; Nathalie Bar, N.; Jarsalé, K.; Choukchou-Braham, N. Catalyzed reaction of enaminonitrile with primary amines by $SbF_3$: synthesis of new 2-aminosubstituted-pyridine-fused δ-lactones. *Arkivok* **2018**, 65–74, doi:10.24820/ark.5550190.p010.495.
2. Bektas, T.; Dimitra, D.; Atalay, S.; Munevver, S.; Moschos, P. Antimicrobial and antioxidant activity of essential oil and various extracts of Salvia tomentosa Miller. *Food Chem.* **2005**, *90*, 333–340, doi:10.1016/j.foodchem.2003.09.013.
3. Shen, Q.; Zhang, B.; Xu, R.; Wang, Y.; Ding, X.; Li, P. Antioxidant activity in vitro of the selenium-contained protein from the Se-enriched Bifidobacterium animalis 01. *Anaerobe* **2010**, *16*, 380–386, doi:10.1016/j.anaerobe.2010.06.006.
4. Remmal, A.; Bouchikhi, T.; Rhayour, K.; Rhayour, K. Improved method for determination of antimicrobial activity of essential oils in agar medium. *J. Essent. Oil Res.* **2011**, *5*, 179–184, doi:10.1080/10412905.1993.9698197.
5. Bijondi, D.; Cianci, P.; Geraci, C.; Ruberto, G. Antimicrobial and chemical composition of essential oils from Sicilian aromatic plants. *Flavour Fragr. J.* **1993**, *8*, 331–377, doi:10.1002/ffj.2730080608.