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Proceeding Paper

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

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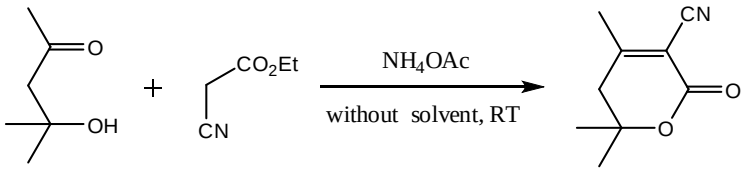
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021. Available online: https://ecsoc-25.sciforum.net/.

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

1. Introduction

Substituted 2-aminopyridine δ-lactone derivatives were achieved. 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (1) was synthesised from 4-hydroxy-4-methylpen tan-2-one [1] (Figure 1), followed by its transformation in enaminonitrile with DMFDMA [1].

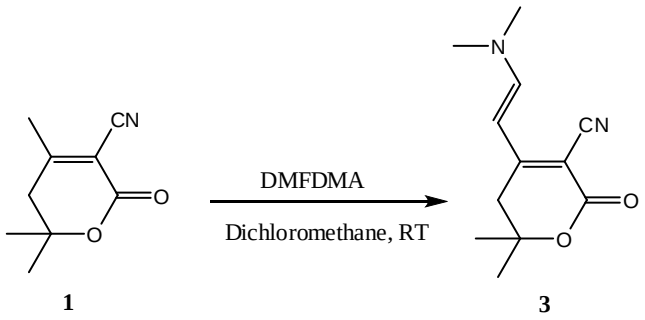


2 **1**

Figure 1. Synthesis of 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile **1**.

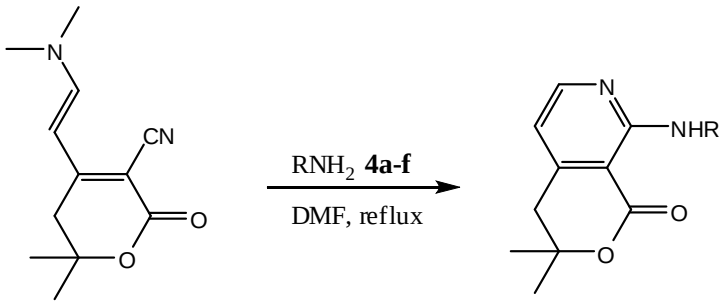
The compound **3** was prepared by the reaction of δ-lactone nitrile «4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile » **1** with dimethylformamide dimethylacetal DMFDMA in stoichiometric amounts. The reaction was performed at room temperature during 24 h and afforded good overall yield (72%)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

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**, according Figure 3, results are reported in Table 1.



1 **3**

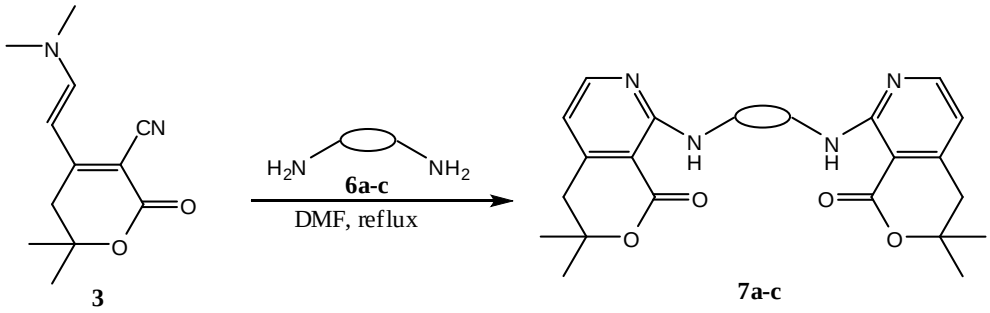
Figure 2. Synthesis of enaminolactone nitrile **3**.



3 **5a-f**

Figure 3. Synthesis of 2-aminopyridines 5a-f from enaminolactone nitrile 3.

The reactions between 1 equiv of diamines **6a–c** with 2 equiv of enaminolactone nitrile **3** were performed. The mixture was refluxed in DMF during 6 h. 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 (Figure 4, Table 2).

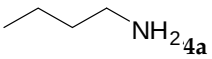
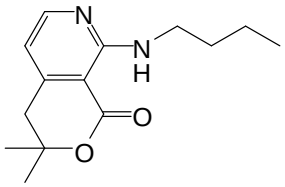
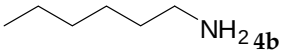
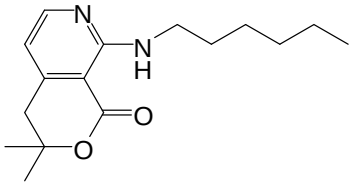
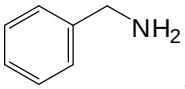
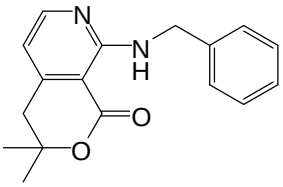
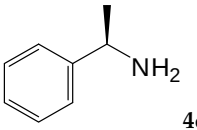
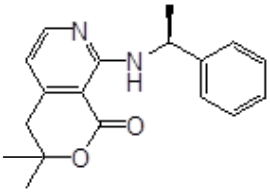
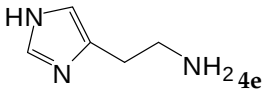
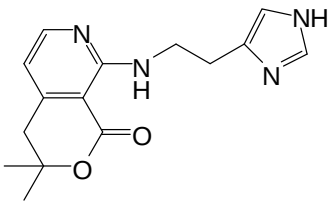
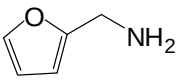
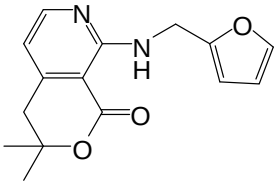


3 **7a-c**

Figure 4. Synthesis of new bis-(2-aminopyridines) **7a–c**.

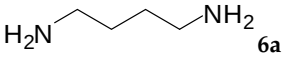
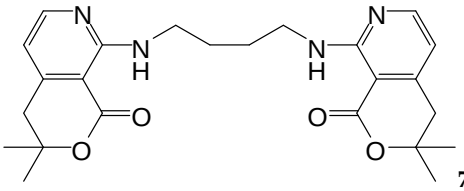
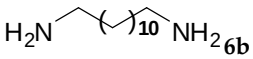
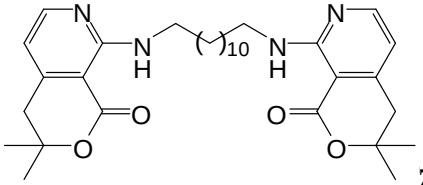
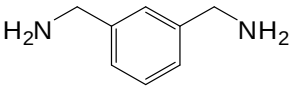
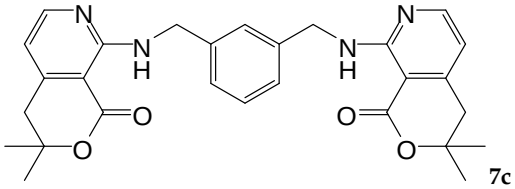
The structure of the compounds **7a–c** was confirmed by spectral data (IR, ^{1}H NMR and ^{13}CNMR).

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 were characterised by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR and MS).

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-aminopyrid ines 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 [4] 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 **7b** 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.

4. Experimental

In the supplementary informations:

(A) Synthesis and Screening of Antioxidant Potential
(B) Screening of antibacterial and antifungal properties of the compounds.

5. Conclusions

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

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ecsoc-25-11709/s1.

Author Contributions: Conceptualization, D.V.; Investigation, F.S. and N.B.; Writing—Original draft, N.B. and D.V.; Writing—Review and editing, N.C., N.B. and D.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Supplementary Informations in English (parts A and B) https://hal-normandie-univ-archives-ouvertes-fr.ezproxy.u-pec.fr/hal-03510414/document.

Conflicts of Interest: The authors declare no conflict of interest.

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