chemistry proceedings

MDPI

Proceeding Paper

In Situ *one pot* Hemi-Synthesis of New 2-Pyridone Derivatives †

Maamar Haffas [1,2,3,*], Naima Benkiki [1], Ramzi Maadadi [2,3], Oualid Talhi [3], Chafai Boukentoucha [4], Farid Chebrouk [3] and Zahia Kabouche [2]

[1] Laboratoire de Recherche Biotechnologie des Molécules Bioactives et de la Physiopathologie Cellulaire, Faculté des Sciences de la Nature et de la vie de l'université de BATNA 2 Algérie; benkiki_n@yahoo.fr
[2] Laboratoire d'Obtention des Substances Thérapeutiques (LOST), Département de chimie, Campus Chaabet-Ersas, Université des frères Mentouri-Constantine, Constantine 25000, Algérie; rmaadadi@gmail.com (R.M.); zahiakabouche@gmail.com (Z.K.)
[3] Centre de Recherche Scientifique et Technique en Analyses Physico—Chimiques, BP 384, Zone Industrielle Bou-Ismail RP 42004 Bou Ismaïl, Tipaza Alegrie; oualid_talhi@yahoo.fr (O.T.); chebroukfarid@yahoo.fr (F.C.)
[4] Unité de Recherche de Chimie de l'Environnement et Moléculaire Structurale CHEMS, Université des Frères Mentouri Constantine 1, Constantine 25000, Algerie; Cboukent@gmail.com
* Correspondence: maamar.haffas@univ-batna.dz
† Presented at 25th International Electronic Conference on Synthetic Organic Chemistry 15–30 November 2021.

Abstract: New 2-pyridone derivatives were hemi-synthetised in situ using essential oils of endemic Algerian plants; *Ammodaucus Leucotrichus and eucalyptus citriodora* as source of chiral aldehydes (perillaldehyde and citronellal respectively). The *one pot* reaction was carried out in Ethanol including cyanoacetohydrazide, essential oil, and malononitrile. The reaction mixture was catalysed by potassium carbonate. In the present work, two new compounds of highly functionalized 2-pyridones were obtained as privileged medicinal scaffolds. The structures of 2-pyridone derivatives were confirmed by ^{1}H NMR, ^{13}C and 2D.

Keywords: *one pot*; essential oil; 2-pyridone; Hemi-Synthesis; NMR analysis

Citation: Haffas, M.; Benkiki, N.; Maadadi, R.; Talhi, O.; Boukentoucha, C.; Chebrouk, F.; Kabouche, Z. In Situ *one pot* Hemi-Synthesis of New 2-Pyridone Derivatives. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2021

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

1. Introduction

During the last decade, researchers have attached a great importance to hemi-synthesis reactions [1–3], where a new compounds design strategy based on the combination of functional classes and terpene compounds contained as major constituents in essential oils of medicinal plants has been developed. In fact, researchers depend as much as possible in the organic synthesis of their biologically active compounds on the *one-pot* method, to make short effort and time.

Several documented studies have revealed that pyridones derivatives possess a range of useful biological activities, being antiviral, anti-HIV and anti-cancer [4–6] Figure 1. In this context, an efficient and economical method by hemisynthesis reactions; two novel chiral2-pyridone derivatives: 1,6-diamino-2-oxo-4-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) and 1,6-diamino-4-(2,6-dimethylhept-5-en-1-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2**) were synthetised. The multi-component reactions were carried out in situ, using *Ammodaucus Leucotrichus* (80% perillaldehyde) and *Eucalyptus citriodora* (70% citronellal) essential oils as substrates.

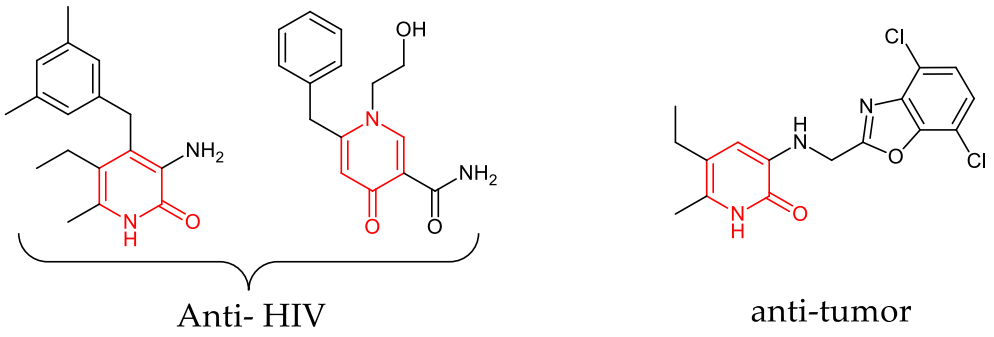


Figure 1. Therapeutic effect of 2-pyridone derivatives.

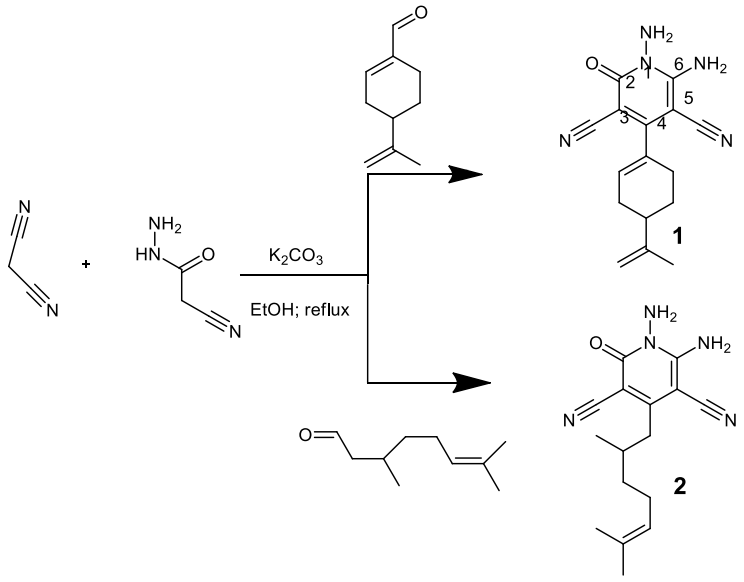
2. Methods and Materials

2.1. Instrumentation and Reagents

All commercially available chemicals and reagents were purchased from Merck Co. and used without further purification. Melting points were measured with an Electrothermal 9200 apparatus. NMR spectra were recorded on a Bruker AVANCE 400 spectrometer (Bruker, Wissembourg, France, 400 MHz for ^{1}H and 100 MHz for ^{13}C). NMR spectra were obtained in $CDCl_3$ and DMSO-d_6.

2.2. Synthesis of 2-Pyridones

The compounds (1) and (2) were prepared by adding *Ammodaucus. leucotrichus* essential oil (1 mmol of perillaldehyde, 185 mg of the crude oil) or *eucalyptus citriodora* essential oil (1 mmol of citronellal, 0.235 mL of the crude oil) respectively to malononitrile (66 mg, 1 mmol), cyanoacetohydrazide (99 mg, 1 mmol), and K_2CO_3 (138mg, 1 mmol)in EtOH (7 mL). The final mixture was stirred at 80 °C for 4 h; then when the reaction was completed (monitored by TLC), the reaction solution was cooled and neutralized with diluted HCl then poured into water. The solid that precipitated was filtered, washed with water, dried and recrystallized in MeOH to afford the product (1) and (2) (yield 91% and 83% respectively).

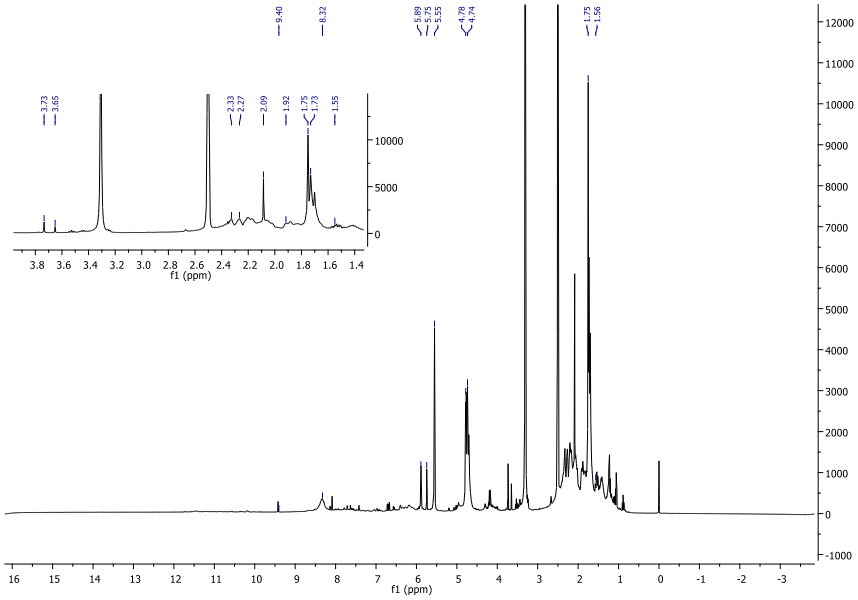


Scheme 1. Formation of pyridine derivatives 1 and 2.

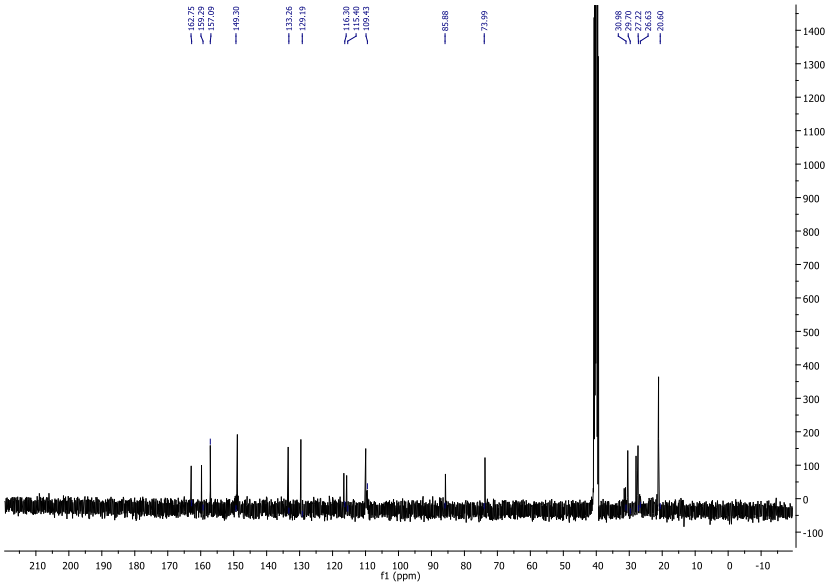
3. Results and Discussions

We hemi synthesized in a single step (one pot) two new 2-pyridone derivatives containing a terpene moiety according to the method used by Ramadan A.M. and all [7], from three compounds; malononitrile, cyanoacetohydrazide and an essential oil containing mainly oxygenated terpene (aldehyde in this Case). The structures of compounds **1** and **2** were characterized from their ^{1}H NMR and ^{13}C NMR spectroscopic data Schemes 3 and 4.

The investigation of the ^{1}H NMR spectra to the product **1** showed that, signals at δ 5.55 and 8.33 ppm confirmed the presence of N–NH_2 and NH_2 amino group protons respectively. A singlet appeared at δ 1.75 ppm is assigned to methyl group protons CH_3. The proton =CH intra-cyclic and extra-cyclic of the terpene moieties reflect signals at (δ 5.75-5.88 ppm, doublet) and at δ 4.74 ppm respectively. ^{13}C NMR spectra showed signals at 159, 157 and 162 ppm assigned to the carbons C-NH_2, C-4, and the carbonyl group in the pyridone ring respectively.



Scheme 3. ^{1}H NMR spectra of 2-pyridone derivatives **1.**



Scheme 4. ^{13}C NMR spectra of 2-pyridone derivatives **1.**

4. Conclusions

In summary, we have reported the first *one pot* hemi-synthesis of new pyridone derivatives using essential oils as source of chiral aldehydes, the reactions were carried out in situ without any prior isolation or purification. This method is advantageously applicable to generate chiral compounds avoiding the use of expensive chiral catalyst and isolated natural compounds. In many molecules of biological and pharmaceutical fields, pyridones can be synthesized by different chemical protocols. From our point of view, it will be interesting to continue the investigation in the results of hemisynthesis by carrying out the biological activity of the obtained compounds, according to the results of the bibliography.

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

References

1. Chebrouk: F.; Madani, K.; Cherfaoui, B.; Boukenna, L.; Válega, M.; Mendes, R.F.; Paz, F.A.A.; Bachari, K.; Talhi, O.; Silva, A.M.S. Hemi-Synthesis of Chiral Imine, Benzimidazole and Benzodiazepines from Essential Oil of *Ammodaucus leucotrichus subsp. Leucotrichus*. *Molecules* **2019**, *24*, 975.
2. Khalfaoui, M.; Chebrouk, F.; Ziani, B.E.C.; Bennamane, N.; Cherfaoui, B.; Frites, W.; Válega, M.; Mendes, R.F.; Paz, F.A.A.; Chebout, R.; et al. Hemi-synthesis, in-vitro and in-silico bioactivities of new chiral-Schiff bases and benzodiazepine derivatives from *Ammodaucus leucotrichus* (S)-perillaldehyde. *J. Mol. Struct.* **2021**, *1241*, 130690.
3. Sameut, A.; Zandouche, S.Y.; Boumaza, C.; Digues, C.; Ziani, B.E.C. Chemical Synthesis and Hemi-Synthesis of Novel Benzimidazoles Derivatives Using Microwave- Assisted Process: Chemical Characterization, Bioactivities and Molecular Docking. *Chem. Proc*. **2020**, *3*, 71.
4. Nicolas, B. Vers La synthèse totale biomimétique de la lodopyridone et l'étude phytochimique de Lycopodiellacernua et de Nitrariaretusa. Ph.D. Thesis, PARIS-SACLAY University, Paris, France, 2 December 2015.
5. Xie, W.; Wu, Y.; Zhang, J.; Mei, Q.; Zhang, Y.; Zhu, N.; Liu, R.; Zhang, H. Design, synthesis and biological evaluations of novel pyridone-thiazole hybrid molecules as antitumor agents. *Eur. J. Med. Chem.* **2018**, *145*, 35–40, doi:10.1016/j.ejmech.2017.12.038.
6. Masaret, G.S., Synthesis, Docking and Antihypertensive Activity of Pyridone Derivatives. *ChemistrySelect* **2020**, *5*, 13995–14003.
7. Mekheimer, R.A.; Al-Sheikh, M.A.; Medrasi, H.Y.; Alsofyani, N.H.H. A Novel Synthesis of Highly Functionalized Pyridines by a *One-Pot*, Three-Component Tandem Reaction of Aldehydes, Malononitrile and N-Alkyl-2-cyanoacetamides under Microwave Irradiation. *Molecules* **2018**, *23*, 619.