GREEN CHEMISTRY TOWARDS THE SYNTHESIS OF SOME 2-PYRROLIDINONE DERIVATIVES

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TÓM TẮT

TỔNG HỢP MỘT SỐ DẪN XUẤT CỦA 2-PYRROLIDINONE THEO CON ĐƯỜNG HÓA HỌC XANH

Ba dẫn xuất của 2-pyrrolidinone được tổng hợp dựa vào phản ứng nhiều thành phần, sử dụng dung môi thân thiện với môi trường là ethanol. Một số thuận lợi của phản ứng nhiều thành phần là cách tiến hành thí nghiệm đơn giản, sử dụng nguyên liệu giá thành thấp và khá phổ biến. Bên cạnh đó, cấu trúc của ba hợp chất này được giải thích dựa vào các phương pháp phổ như phổ hồng ngoại (IR), phổ khối lượng (MS) và phổ cộng hưởng từ hạt nhân (NMR).

***Từ khóa**: 2- pyrrolidinone derivatives, one-pot multi-component reaction.*

1. INTRODUCTION

Throughout the development of organic chemistry, heterocyclic compounds always play an extremely important role. They are widely used in many fields of science, technology and life. Over the past few decades, this field has developed strongly and been studied systematically, completely in detail on the basis of the modern scientific knowledge. Annually, the number of articles about the heterocyclic compounds accounts for more than half of the total organic chemistry work published in the world's official journals. Among them, the derivatives of 2-pyrrolidinone have enormous potentials for application in pharmaceutical and agrochemical industries.

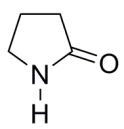


Fig 1. The structure of 2-pyrrolidinone

2-Pyrrolidinone is a type of lactam compound with a 5-membered ring including four carbon atoms and a nitrogen atom [1]. The derivatives of 2-pyrrolidinone are the important compounds found in various pharmaceutical products. For instance, tobacco contains an alkaloid named cotinine (1), which is a major metabolite of nicotine. It can be used to treat depression, schizophrenia, Alzheimer's disease and Parkinson's disease [2]. Doxapram (2) stimulates the increase in tidal volume and the respiratory rate [3]. Pramiracetam (3), which is a central nervous system stimulant and nootropic agent, used as a treatment for memory and attention deficits in aging people with neurodegenerative and vascular dementias [4].

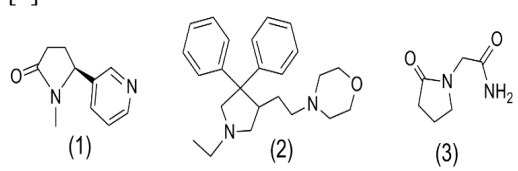
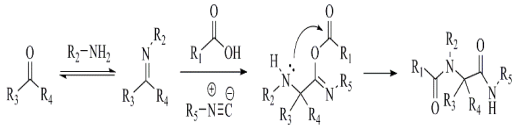


Fig 2. Some 2-pyrrolidinone derivatives in medicine

However, the synthesis of 2-pyrrolidinone derivatives in large quantities by conventional

methods is quite difficult. Therefore, we studied the application of multiple-component reactions (MCRs) - a new trend attracting much interest in organic synthesis - in the preparation of such compounds. MCRs are chemical reactions in which three or more primary substances react together to produce a target product. These reactions depend on some conditions: solvent, temperature, catalyst and initial concentration [5]. The specificity of this kind of reaction is carrying out simple experiment as well as using low cost, relatively common and environmentally friendly materials [6]. Appearing firstly in 1850 with the α-amino acid synthesis conducted by Adolph Strecker [7]; but until 1959, the popularity of this type of reaction increased rapidly after the emergence of a four-component reaction (between ketone or aldehyde with amine, isocyanide and carboxylic acid to form bis-amide) made by Ugi and his colleagues [8].



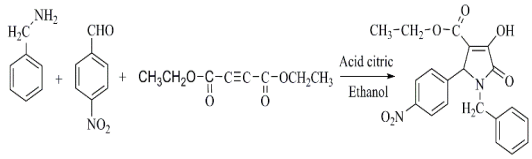
Scheme 1. The mechanistic path of Ugi reaction [8]

In our study, we performed the synthesis of several 2-pyrrolidinone compounds by applying the multi-component reaction with eco-friendly solvent.

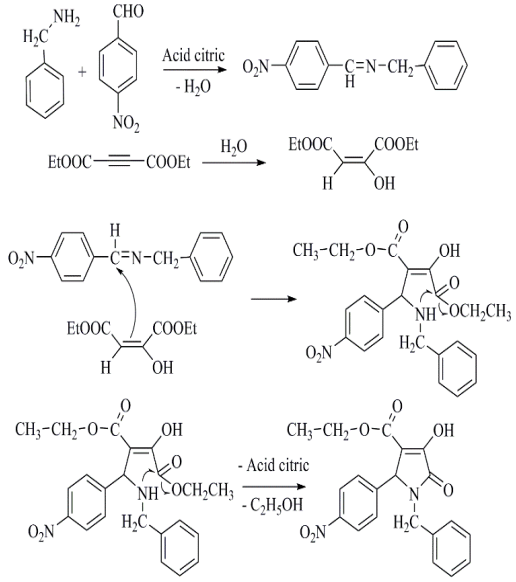
2. EXPERIMENTAL PROCEDURES

2.1. General procedure for the preparation of 2-pyrrolidinone

A solution of amine (1 mmol), aldehyde (1 mmol), citric acid (2 mmol) and ethanol (2 ml) was added to a round-bottom flask and magnetically stirred 3 hours at room temperature to form imine. After that, diethyl acetylenedicarboxylate (0.16 ml) was added to the mixture. The formation of imine as well as the progress of the reaction were monitored by thin layer chromatography (n-hexane : ethyl acetate = 5 : 3.5). After completion of the reaction, solvent was removed under reduced pressure and column chromatography was used to obtain 2-pyrrolidinone derivatives. In order to remove citric acid, product was recrystallized in hot ethanol (at 80°C) [9].



Scheme 2. The synthesis of 2-pyrrolidinone derivative from benzylamine and 4-nitrobenzaldehyde



Scheme 3. The mechanistic path for the synthesis of 2-pyrrolidinone compound from benzylamine and 4-nitrobenzaldehyde [9]

2.2. Chemicals and experimental methods

All the chemicals including benzylamine, *m*-nitroaniline, benzaldehyde, *p*-tolualdehyde, 4-nitrobenzaldehyde, diethyl acetylenedicarboxylate, citric acid, ethanol, chlorofom, dichloromethane, n-hexane, ethyl acetate were purchased from Merck (Germany) and ACROS (Belgium). For column chromatography, 70–230 mesh silica 60 (E. M. Merck) was used as the stationary phase.

NMR spectra were acquired with Ascend Bruker 500 MHz spectrometer and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (TMS) or the internal (NMR) solvent signals. Mass spectra were recorded with LTQ Orbitrap XL (ESI-MS). Infrared spectra were recorded with SHIMADU 1800 FTIR spectrometer.

3. RESULTS AND DISCUSSION

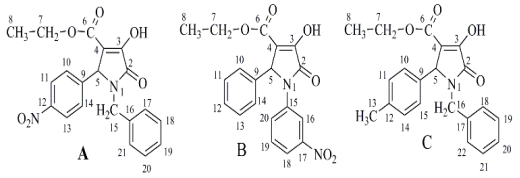


Fig 3. The structure of three 2-pyrrolidinone compounds

Table 1. The yields of three 2-pyrrolidinone compounds

Product	Amine	Aldehyde	Yield
A	$C_6H_5CH_2$-NH_2	*p*-$NO_2C_6H_4$-CHO	77.49%
B	*m*-$NO_2C_6H_4$-NH_2	C_6H_5-CHO	95.38%
C	$C_6H_5CH_2$-NH_2	*p*-$CH_3C_6H_4$-CHO	80.63%

Compound **A**, white powder solid. **ESI-MS**: m/z 383.1239 $[M + H]^+$. **IR**: 3136.25; 2980.02; 2920.23; 1791.87; 1701.22; 1689.64; 1680.00; 1595.13; 1517.98; 1373.32; 1344.38; 1226.73; 1029.99; 821.68; 759.95; 690.52 cm^{-1}. **^{1}H-NMR** (DMSO-d_6, 500MHz) δ_H ppm: 12.03 (1H, s); 8.16 (2H, d); 7.42 (2H, d); 7.26 (3H, m); 7.06 (2H, d);
5.18 (1H, s); 4.80 (1H, d); 3.96 (2H, q); 3.81 (1H, d); 1.03 (3H, t). **^{13}C-NMR** (DMSO-d_6, 125MHz) δ_C ppm: 165.37; 162.17; 154.58; 147.81; 144.53; 136.69; 129.78; 129.03; 128.25; 127.90; 124.10; 111.46; 60.12; 60.06; 44.67; 14.41.

Compound **B**, white powder solid. **ESI-MS**: m/z 369.1077 $[M - H]^+$. **IR**: 3118.90; 2980.02; 2922.16; 1747.51; 1701.21; 1689.64; 1676.14; 1573.91; 1516.05; 1363.67; 1344.38; 1217.08; 1056.99; 821.68; 758.02; 698.23 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 500MHz) δ_H ppm: 9.12 (1H, s); 8.31 (1H, s); 8.08 (1H, d); 7.94 (1H, d); 7.46 (1H, t); 7.27 (5H, m); 5.80 (1H, s); 4.20 (2H, q); 1.19 (3H, t). **^{13}C-NMR** ($CDCl_3$, 125MHz) δ_C ppm: 165.24; 163.08; 156.31; 148.56; 137.69; 134.34; 130.05; 129.17; 129.12; 127.57; 127.36; 120.17; 116.06; 113.92; 61.73; 61.41; 14.04

Compound **C**, white powder solid. **ESI-MS**: m/z 352.1544 $[M + H]^+$. **IR**: 3300.20; 3093.82; 2987.74; 1867.09; 1716.65; 1681.93; 1653.00; 1590.00; 1523.75; 1369.46; 1346.31; 1213.23; 1022.27; 869.90; 763.81; 693.23 cm^{-1}. **^{1}H-NMR** ($CDCl_3$, 500MHz) δ_H ppm: 9.06 (1H, s); 7.30 (3H, m); 7.16 (2H, d); 7.12 (2H, dd); 6.99 (2H, d); 5.20 (1H, d); 4.85 (1H, s); 4.08 (2H, q); 3.54 (1H, d); 2.37 (3H, s); 1.08 (3H, t). **^{13}C-NMR** ($CDCl_3$, 125MHz) δ_C ppm: 165.83; 163.85; 158.01; 139.04; 136.80; 131.79; 129.92; 129.20; 128.94; 128.23; 128.11; 113.69; 61.38; 59.79; 44.27; 21.63; 14.27.

Regarding the IR spectrum of compound **A**, the peaks at 3136.25 cm^{-1} and 1680.00 cm^{-1} corresponded with the stretching vibration of the O-H and C=C bonds. The stretching vibration of C=O and C-O bonds belonging to the ester group were represented by two peaks located at 1701.22 cm^{-1} and 1226.73 cm^{-1}, respectively. In addition, the stretching vibration of the C=O bond in ketone group was described by the peak at 1689.64 cm^{-1}. Moreover, the peaks corresponding with the stretching vibration of the carbon-carbon bonds in benzene ring appeared at 1517.98 cm^{-1} and 1595.13 cm^{-1}. Finally, no peak showed for the present of the N-H bond of the primary and secondary amine, amide (in range of 3300 – 3500 cm^{-1}) and nitrile (2250 cm^{-1}). As a result, nitrogen atom in compound A constituted tertiary amine that was not present in the IR spectrum.

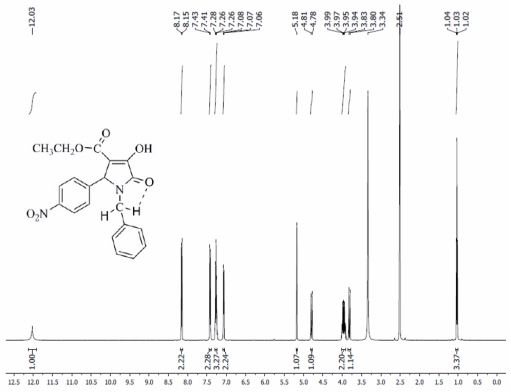


*Fig 4. ^{1}H-NMR spectrum of compound **A***

The ^{1}H-NMR spectrum of 2-pyrrolidinone derivative **A** formed from benzylamine and 4-nitrobenzaldehyde appears the peaks corresponding to all hydrogen atoms in the molecule. First of all, the peak of the proton belonging to the OH group was a singlet with the wide base and low intensity at δ_H 12.03 ppm. Besides, the peaks corresponding to two and three hydrogen atoms of methylene group at position 7 and methyl group at position 8 were present at δ_H 4.01 ppm in quartet and at

δ_H 1.03 ppm in triplet, respectively. Additionally, the proton of the CH group at position 5 was shown by a singlet at δ_H 5.18 ppm. The peaks corresponding to nine hydrogen atoms of two benzene rings were located in the range of δ_H from 7.06 ppm to 8.17 ppm. Lastly, at δ_H 4.80 and 3.81 ppm, there were two doublets characterizing the protons of the CH_2 group linking to the monosubstituted benzene ring. These protons were not equivalent and they had spin-spin interactions with the other because one of them linked with the oxygen atom of the carbonyl group by the intramolecular hydrogen bond. Thus, the doublet at δ_H 4.80 ppm corresponded with the proton participating in the above mentioned bond and another doublet at δ_H 3.81 ppm belonged to the remaining hydrogen atom. The structure of compound **A** was also confirmed by the ^{13}C-NMR nuclear magnetic resonance spectroscopic measurement. In this spectrum, the peaks corresponding with the carbon atoms at position 2, 3 and 6 appeared at δ_C 154.59 ppm, 162.19 ppm and 165.39 ppm. In addition, the carbon atoms of the C=C bond and two benzene rings were represented by the peaks in the region of δ_C 111.46 to 147.81 ppm. At δ_C 14.41 ppm and 60.06 ppm, there were two peaks corresponding with the carbon atoms belonging to the CH_3 and CH_2 groups at position 8 and 7. Moreover, the peak of the carbon atom at position 5 had the chemical shift at 60.13 ppm. Along with that, the peak located at δ_C 44.67 ppm was characteristic of the carbon atom at position 15, which created a bond with the nitrogen atom. Because the electronegativity of the nitrogen is less than that of the oxygen, its chemical shift was smaller than that of the carbon at position 7.

The IR, ^{1}H-NMR and ^{13}C-NMR spectra of compound **B** and **C** were similar to compound **A**. However, compared to product **A**, the composition of compound **C** had a CH_3 group which directly linked to the disubstituted benzene ring. While the carbon atom at this position was characterized by the peak at 21.63 ppm, three hydrogen atoms of this group corresponded with a peak in the singlet form at δ_H 2.37 ppm.

4. CONCLUSIONS

The synthesis of substituted 3-pyrroline-2-ones *via* multicomponent reaction using eco-friendly solvent and citric acid as a green additive is a useful procedure in modern synthetic methodologies. The structure of target compounds was confirmed by modern spectroscopic methods: FTIR, ESI-MS and NMR.

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