THE STUDY SYNTHESIS OF NIFEDIPINE - CALCIUM ANTAGONIST

Roxana Blajovan, Dorina Modra

West University of Timișoara, Faculty of Chemistry-Biology-Geography, Department of Biology-Chemistry, Pestalozzi Street, 16, Timișoara, 300115, Romania

Received: 25 September 2013 Modified: 3 October 2013 Accepted: 18 October 2013

Summary

Hypertension is the most common cardiovascular disease in developed countries, together with ischemic heart disease (IHD), heart failure (CI) and stroke group performed the underlying disease, "the explosion" cardiovascular mortality XXI century. Benefits of antihypertensive treatment in all groups meet higher in hypertensive patients: the young, the elderly, coronary diabetic patients with chronic kidney disease, etc.. The benefit is substantial in many forms of secondary hypertension, which may become curable by pharmacological therapy, interventional or surgical. This paper aims to conduct a study of calcium beta blocker first generation, an important medical concern, nifedipine, known as dihydropyridine first recommended in the treatment of hypertension. We also studied the synthesis methods used in the laboratory and results syntheses carried out to follow the influence of variations of different parameters.

Keywords: nifedipine, treatment of hypertension, calcium antagonist

Introduction

Nifedipine is a calcium antagonist of type 1,4 - dihydropyridine. Calcium antagonists oppose the entry of calcium into cells, reduce the influx of calcium ions through the slow calcium channels in the cell.

The dihydropyridines are widely used for their vascular relaxation property, especially angina, chronic stable angina, and hypertension.

For many years it was considered that the dihydropyridine calcium antagonist
lowers blood pressure by blocking calcium influx predominantly at type calcium channels L. This is supported by recent studies showing that dihydropyridines cause the release of nitric oxide in the vascular endothelium leading to vasodilatation. [5] They have powerful anti-hypertensive effects.

In search of active drugs for the treatment of coronary insufficiency, F. Bosset synthesized in 1966 nifedipine and nifedipine in 1975 became one of the most available drugs to treat cardiovascular disease. [7] Nifedipine was initially used in atypical cases induced by angina pectoris.

Nifedipine acts mainly on smooth muscle in the wall of the coronary and peripheral arteries. [8, 9] In the heart, nifedipine dilated coronary arteries, especially broad conductance vessels. Nifedipine reduces vascular smooth muscle tone in the coronary arteries and prevents vasospasm. The result is increased poststenotic blood flow and increased oxygen intake. In parallel, nifedipine reduces oxygen demand, decreasing peripheral resistance (afterload). In long-term treatment, nifedipine can prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine reduces the tone of smooth muscle in the arterioles, decreasing peripheral resistance and consequently blood pressure. Early treatment may be a transient increase in heart rate and cardiac volume per minute. However, this increase does not compensate for vasodilation. Nifedipine increases the excretion of sodium and water in both the short-term treatment and long term. Lowering blood is especially pronounced in hypertensive patients. In Raynaud syndrome, nifedipine can prevent or reduce vasospasm in the fingers. [10]

Nifedipine is a calcium antagonist with specific and effective action, especially as a smooth muscle relaxant and peripheral coronary pressure. [11, 12] Through this mechanism, in pectoral angina the load is reduced left ventricular dilatation produces submaximal coronary arteries affected, protecting the heart against coronary artery spasm and improving perfusion of ischemic myocardium. [13, 10]

Nifedipine reduces the frequency of painful crises and ischemic ECG changes, independent of the relative contribution of coronary artery spasm or atherosclerosis. [14] The product reduces blood pressure, the rate of decrease being proportional to baseline. In the case of normotensive, nifedipine has a low or no action on the blood pressure.

Nifedipine in terms of the chemical is 2,6-dimethyl-3,5-dimetoxicarbonil-4-o-nitrophenyl-1,4-dihydropyridine and has the empirical formula C_{17}H_{18}N_{2}O_{6}. It is used as an extended release capsule of tablet. Nifedipine is a yellow crystalline powder, which when exposed to light or ultraviolet light is converted to a derivative nitrosofenilpiridina. [15]

There is much research showing the properties, crystal structure and multiple uses of nifedipine and its derivatives. [16, 17] The stability of antihypertensive nifedipine has been studied by various experimental solid state NMR metode spectrometrie $^1$H-$^{14}$N NMR-
NQR and through density functional theory, etc. [18]

The condensation of aldehydes, ethyl acetoacetate and ammonium acetate, may be made by ultrasonic irradiation, and solvent-free catalyst at room temperature to give 1,4-dihydropyridines in high yields of 82 - 99%. Compared with conventional methods, the main advantages of this procedure are milder conditions, shorter reaction time and higher yields. [19]

A variant of nifedipine used for the synthesis of 2-nitrobenzaldehyde, methyl acetoacetic acid methyl ester, methanol, ammonia or ammonium salt. [20, 21] The mixture is heated for several hours, cooled and the product filtered off (yellow crystalline product).

Synthesis and characterization of nifedipine have been reported in many researches, but the main objective of this paper is to optimize the return on pursuing the effects of various parameters of the reaction: molar ratio of reactants, reaction time, solvent type reaction.

**Materials and Methods**

**Reagents and materials**

For the synthesis of 2,6-dimethyl-3,5-dimetoxicarbonil-4-o-nitrophenyl-1,4-dihydropyridine reagents used were: 2-nitrobenzaldehyde (99%) (Sigma-Aldrich), methyl acetylacetate (99%) (Sigma-Aldrich), methanol (99.8%) (Sigma-Aldrich), ammonia (min. 25%) (Merck). For washing of the crude product using ethyl ether (99%) (Sigma-Aldrich), and the recrystallization ethanol (SC Chimopar SA Romania), n-propanol (Merck) and isopropanol (SC Chimopar SA Romania).

Alcohols and other materials used are of analytical grade and used without special treatment.

Melting points were determined in open tube capillary method using an apparatus "Melting Point Meter" KR-P1, from the company Kruss Optronic GmbH. IR spectra were recorded using a Perkin Elmer FT-IR spectrophotometer - Spectrum 100.

**Synthesis**

The method used in the laboratory synthesis involves the condensation of 2-nitrobenzaldehyde with methyl acetylacetate.

A mixture of 2-nitrobenzaldehyde, methyl acetylacetate is dissolved in methanol. Ammonia was added, the mixture heated at reflux. After completion the reaction mixture was cooled and precipitated pyridine derivative.

Yellow precipitate is filtered under vacuum Buchner funnel and washed with cold ether. The product thus obtained is purified by recrystallization.
The reaction is:

\[ \text{2-nitrobenzaldehyde : methyl acetoacetate} \]

The syntheses were carried out to find the best conditions for the synthesis of nifedipine as high efficiency.

**Results and Discussion**

The influence of the molar ratio of the reactants

In order to study the influence of the molar ratio of the reactants on the yield of nifedipine have been made in the laboratory synthesis. The syntheses were carried out using methanol as the reaction medium in a proportion of 30% relative to the amount of the reaction mixture. The duration of the synthesis is 6 hours at reflux temperature (65 - 66°C). The ammonia is in all embodiments of the synthesis uses the molar ratio of 2-nitrobenzaldehyde to 7:1. The ratio of reaction of 2-nitrobenzaldehyde: methyl acetoacetate between 1:2 to 1:4. The experimental results obtained are shown in Table I.

### Table I. Experimental results

<table>
<thead>
<tr>
<th>Crt. No.</th>
<th>Molar ratio of reactants</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 2.0</td>
<td>54.2</td>
</tr>
<tr>
<td>2</td>
<td>1 : 2.5</td>
<td>70.5</td>
</tr>
<tr>
<td>3</td>
<td>1 : 3.0</td>
<td>75.3</td>
</tr>
<tr>
<td>4</td>
<td>1 : 4.0</td>
<td>77.8</td>
</tr>
</tbody>
</table>

The results were plotted in Figure 1.
After synthesis it was found that with increasing molar ratio o-nitrobenzaldehyde: acetylacetic methyl nifedipine increases yield. At a molar ratio of o-nitrobenzaldehyde: acetylacetic 1 methyl 4 nifedipine increased yield is only 2.5%, which represents an insignificant amount extra methyl acetylacetic used.

**Influence of synthesis time**

Follow-up duration effect on yield nifedipine synthesis was achieved by performing the reaction of 2-nitrobenzaldehyde with methyl acetilacetatul sinteză. Reaction times vary between 1 hour up to 8 hours.

The molar ratio of o-nitrobenzaldehyde: methyl acetylacetic used was 1:3. The reaction temperature is 65 - 68°C. The amount of methanol used as the reaction medium is 30% on the total amount of the reaction mixture. The ammonia is in all embodiments of the synthesis uses the molar ratio of 2-nitrobenzaldehyde to 7:1.

The experimental data obtained from the synthesis in the laboratory are shown in Table II.

**Table II. The reaction conditions and the yields obtained**

<table>
<thead>
<tr>
<th>Crt.No.</th>
<th>Reaction time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>45.8</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>52.7</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>60.5</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>75.8</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>85.2</td>
</tr>
</tbody>
</table>

In Figure 2 graphically experimental data are presented.

**Figure 2. The variation of the yield depending on the reaction time**

From the graphical representation is an increase of the yield of nifedipine with increasing time condensation of dew is the best time of 8:00.

In order to observe changes in the yield of various parameters to be used according to the embodiment 6 hours of reaction, because in this case the yield is 75.8%, favorable
conditions sufficient for the determination of the synthesis.

_The influence of the solvent used in the synthesis_

To determine the influence of the solvent used in the synthesis of nifedipine, has worked with the following solvents: methanol, ethanol, n-propanol, isopropanol.

The reaction time was 6 hours in all cases, and the molar ratio of the reactants o-nitrobenzaldehyde: acetylacetic of methyl 1:3.

The amount of solvent used as reaction medium is 30% on the total amount of the reaction mixture. The reaction temperature varies depending on the boiling point of the solvent used in the synthesis.

The Table III shows the reaction conditions and experimental results obtained in laboratory syntheses.

**Table III. Experimental conditions and results**

<table>
<thead>
<tr>
<th>Crt. No.</th>
<th>Solvent [%]</th>
<th>Reaction temperature[ºC]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Metanol 30</td>
<td>65-68</td>
<td>75.8</td>
</tr>
<tr>
<td>2.</td>
<td>Etanol 30</td>
<td>78-80</td>
<td>76.9</td>
</tr>
<tr>
<td>3.</td>
<td>n-Propanol 30</td>
<td>97-99</td>
<td>80.1</td>
</tr>
<tr>
<td>4.</td>
<td>Izopropanol 30</td>
<td>82-85</td>
<td>77.4</td>
</tr>
</tbody>
</table>

The experimental data was plotted in Figure 3, graph representing the variation of the yield depending on the solvent used in the reaction.

**Figure 3. The variation of the yield depending on the reaction solvent**

It is found that the yield increases from methanol to n-propanol. This can be explained by the fact that the temperature of reflux (reaction) increases in the same order, because the boiling point of n-propanol is higher than ethanol, methanol respectively. From these data it can be concluded that the reaction occurs with higher yields when working with n-propanol, as the reaction solvent.
The study synthesis of Nifedipine - Calcium Antagonist

The influence of the solvent used for recrystallization

Nifedipine crude after laboratory synthesis is purified by recrystallization operation. As the recrystallization solvent is used ethanol and methanol. The temperature used for the dissolution of the crude product 670°C is the use of methanol, respectively at 770°C using ethanol. Drying is done in the oven at 170°C.

In Table IV are shown the experimental data obtained from recrystallization of nifedipine with methanol, ethanol, respectively.

Table IV. Conditions and experimental data obtained on recrystallization

<table>
<thead>
<tr>
<th>Crt.No.</th>
<th>Solvent for recrystallization</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>metanol</td>
<td>70.2</td>
</tr>
<tr>
<td>2.</td>
<td>ethanol</td>
<td>82.1</td>
</tr>
</tbody>
</table>

Figure 4 shows the yield variation after recrystallization process of nifedipine.

It is noted that when using ethanol as a solvent for recrystallization recrystallization process nifedipine yield increases to 82.1%, compared to only 70.2% when using methanol as solvent recrystallization.

The melting point of nifedipine crude 1650 - 1670°C, while that of nifedipine is purified by recrystallization from 173- 174°C.

Nifedipine obtained and purified by recrystallization has been characterized from the point of view of physico - chemical properties.

The results obtained are as follows: Rock Crystal yellow, m.p. 173 - 174°C, soluble in acetone, methylene chloride, chloroform, ether, slightly soluble in water.

Nifedipine has undergone pure identification reactions:

- Carry out the reaction of the nitro group NO₂ identification of nifedipine by converting the amino group thereof followed by reduction with zinc in the presence of
granules hydrochloric acid. The diazonium salt is engaged N1 - naphthyl ethylene diamine (Bratton - Marsh reagent resulting in a deep red color.

\[
\begin{align*}
R-\text{NH}_2 & \quad \xrightarrow{\text{HNO}_2/\text{HCl}} \quad R-\text{N}^+ = \text{Cl}^{-} + \text{H}_2\text{O} \\
\end{align*}
\]

He IR spectrum of nifedipine is shown in Figure 5.

From IR spectrum can be observed a characteristic absorption bands \(\nu_{\text{N-H}}\) stretching at 3326 cm\(^{-1}\) and the absorption bands at 3236 cm\(^{-1}\) and 2997 cm\(^{-1}\) assigned to the stretching vibrations \(\nu_{\text{C-H}}\) aromatic. It also occurs the characteristic band stretching vibration \(\nu_{\text{C-H}}\) aliphatic, group \(-\text{CH}_3\) specific to the 2841 cm\(^{-1}\). At 1677 cm\(^{-1}\) appears a characteristic intense band \(\nu_{\text{C=O}}\) stretching vibration of ester group. All are present in the spectrum absorption bands attributable to stretching vibrations characteristic group pyridine, 1648 cm\(^{-1}\) (s) and 1617 cm\(^{-1}\) (m). High intensity peak present at 1526 cm\(^{-1}\) is characteristic \(\delta_{\text{N-H}}\) bending vibrations and the 1493 cm\(^{-1}\) present (vi) can be assigned to \(\delta_{\text{C-H}}\) bending vibrations appear in the spectrum peaks at 1308 cm\(^{-1}\) one very intense characteristic symmetrical bending vibrations \(\delta_{\text{C-N}}\) . High intensity bands characteristic \(\nu_{\text{C-O}}\) stretching vibrations occur at 1224 cm\(^{-1}\), and between 829 - 712 cm\(^{-1}\) characteristic stretching vibration band appears \(\nu_{\text{C-N}}\) (specific aryl-nitro) and \(\delta_{\text{C-H}}\) bending vibrations of aromatic substances.

UV spectra showed a maximum absorption at 235.89 nm in methanol solution.

**Conclusion**

Getting nifedipine was achieved in good yield once the influence of the molar ratio of reactants on the yield of nifedipine. It was found that good yield (73.5%) was obtained from version using a molar ratio of o-nitrobenzaldehyde:acetylacetic methyl ammonia.
On increasing the molar ratio of o-nitrobenzaldehyde: acetylacetic methyl is a noticeable increase in yield. Also, it is found that with increasing reaction time, and increase the yield to give good yields of the reaction Laun for 6-8 hours. The solvent was effective in the synthesis of nifedipine is n-propanol, and the crystallization operation may be used such as ethanol and methanol.

Nifedipine is purified, characterized in physico-chemical properties.

References

Blaovan R., Modra D.


