SYNTHESIS AND PROPERTIES OF NEW AZACHALCONES - PRECURSORS OF COMPLEX AND HETEROCYCLIC COMPOUNDS

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Abstract. *A new methodology for the synthesis of azachalcones has been developed to avoid formation of secondary products of dimerization and cyclization, based on the rigorous control of the pH of the reaction medium. The method was applied to obtain 4 substituted azachalcones, which were condensed with 4-ciclohexiletiosemicarbazide. The tridentate ligands containing derived from 2-acetilpyridine thiosemicarbazones were synthesized and characterized by ^{1}H-RMN, ^{13}C-NMR, FTIR spectroscopy. On the basis of the ligand and copper salt was obtained a coordination compound, which will be tested on its biological activity.*

Keywords: *Azachalcone, 2-acetylpyridine, 4-cyclohexylthiosemicarbazide, copper (II) coordinative compounds, biological activity*

Introduction

Chalcones are attributed to the flavonoid family and display several pharmacological activities as anti-inflammatory, antifungal, antiviral, antibacterial, antioxidant [1]. Also, natural chalcones have recently become of increasing interest as yellow and red food dyes [2]. In chalcones, two aromatic rings are linked by the keto-ethylenic group (–CO–CH=CH–). Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity and good pharmacological actions [3]. Nowadays, azachalcones are carried out on their properties as inhibitors of HIV virus and its replication [4]. The purpose of the research is to obtain thiosemicarbazones based on new azachalcones and to complex the compounds obtained with 3d metals, in order to investigate their biological potential.

Particularities of 2-acetylpyridine condensation

The most commonly used but also the most convenient method for synthesis of chalcones is the classic Claisen-Schmidt reaction, which involves condensation of equimolar amounts of benzaldehyde and acetophenone in the presence of aqueous alcoholic alkali [5]. Generally, these reactions result in a high yield. The situation changes radically then occur condensation of substituted benzaldehydes with 2-acetylpyridine, because the presence of nitrogen atom in the aromatic ring leads to an increase in the activity of the methylene component. In this case, the classic Claisen-Schmidt condensation is followed by the Michael addition, between the azachalcone formed and the carbanion of 2-acetylpyridine (Figure 1).

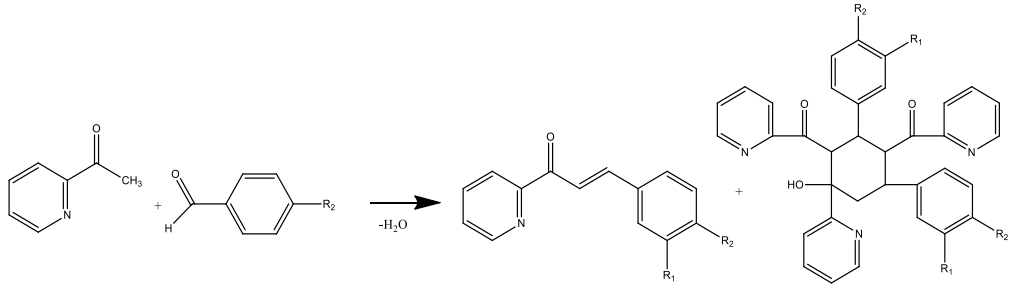


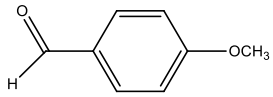
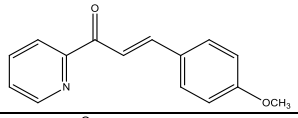
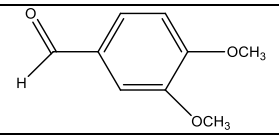
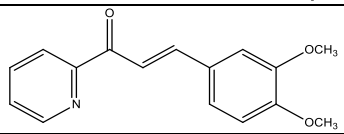
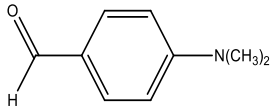
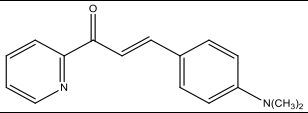
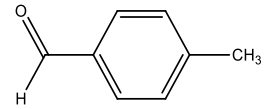
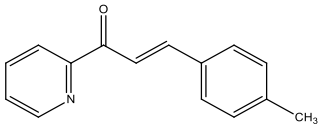
Figure 1. Claisen-Schmidt condensation in presence of 2-acetylpyridine

Experimental

In order to obtain azachalcones without unwanted secondary products, a new synthesis methodology has been developed. Optimal parameters include aqueous-alcoholic environment, temperature of 0°C, and slowly dripping of the aqueous solution of KOH for 40-50 minutes [6]. Following the conditions listed, 4 azachalcones were synthesized on the basis of 2-acetylpyridine, the structure of which was confirmed by spectral methods. It can be seen from Table 1 that the melting temperature of obtained azachalcones (1) and (2) differs significantly with the data described in the literature [7]. We can find that the literature data correspond to the products of dimerization and cyclization.

Table 1

Characterization of azachalcones based on 2-acetylpyridine

N	Substituted benzaldehyde	b.p. or m.p., °C	Azachalcone	η, %	m.p., exp., °C	m.p., lit., °C
1		118 at 10 Torr		71,5	88-89	126
2		160, 10 mm col Hg		72	97-98	138
3		176-177		73	132-133	135-136
4		181, 10 mm col Hg		70,4	79-80	123

It is well known that chalcones can participate in condensation reactions with thiosemicarbazides, forming new biologically active compounds. Research shows that some thiosemicarbazones of 2-formylpyridine exhibit inhibitory properties of HL-60 cell proliferation in human myeloid leukemia, being 40 times more active than cisplatin [8]. The condensation reaction between azachalcone (1) and 4-cyclohexylthiosemicarbazide was performed, with the aim of synthesizing new thiosemicarbazones, with reduced toxicity and selectivity towards tumor cells. Structure of obtained substance was confirmed using monocrystal X-ray diffraction.

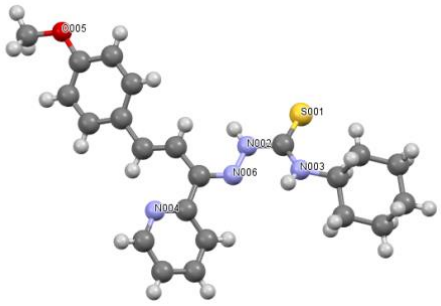


Figure 2. Structure of thiosemicarbazone of azachalcone (ligand HL)

It is known, that anticancer activity is higher for metal complexes, in which organic molecules are ligands, than own activity of organic molecules [9]. The thiosemicarbazone was used to obtain complex copper compounds based on the $Cu(NO_3)_2 \cdot 3H_2O$ salt. The structure for the complex compound $[(Cu(L)NO_3)_2]$ was investigated using X-ray diffraction.

As shown in Figure 3, two copper (II) atoms are linked by means of Sulphur atom bridges, forming symmetrical structure.

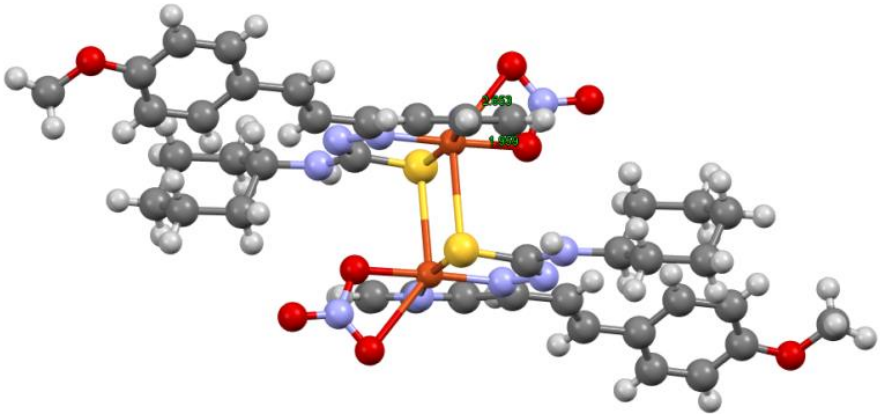


Figure 3. Dimer of [(Cu(L)NO_3)$_2$]

Conclusions

Secondary products of the condensation reaction, obtained by dimerization and cyclization which leads to the decrease of the yield of azachalcones were detected. In order to obtain azachalcones without secondary products, a new synthesis method in the aqueous-alcoholic environment, at 0°C, and dripping of aqueous KOH solution was developed. The structure of monocrystalline thiosemicarbazone of azachalcone, obtained by recrystallization from ethanol, was determined by X-ray diffraction assay. A new coordinative compound was synthesized, not found in the literature in the field, which properties will be studied further.

References:

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