



Editor's choice paper

Activity of immobilized metallic phthalocyanines in the multicomponent synthesis of dihydropyridine derivatives and their subsequent aromatization



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ABSTRACT

Several supported metallo-sulphonated phthalocyanines (FePcS-NH₂-SiO₂, CoPcS-NH₂-SiO₂, and CuPcS-NH₂-SiO₂) and iron hexadecachlorinated phthalocyanines (FePcCl₁₆-NH₂-SiO₂ and FePcCl₁₆-NH₂-SBA-15) were synthesized and evaluated as alternative catalysts for a green multicomponent Hantzsch reaction between an aromatic aldehyde, methyl or ethylacetoacetate and ammonium acetate to obtain the corresponding dihydropyridines or phenylpyridines depending on the reaction conditions. High selectivities (over 80%) to the 2-phenylpyridines, under oxidant and solvent free conditions at room temperature were obtained. While the formation of 1,4-dihydropyridine derivatives were favored at temperatures above 45 °C (selectivities around of 50%). In addition, the 1,4-dihydropyridine derivatives were aromatized to the corresponding pyridines using *t*-BuOOH as oxidant, acetonitrile as solvent and at a reaction temperature of 50 °C.

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1. Introduction

The synthesis of nitrogen-heterocyclic compounds, such as dihydropyridines and pyridines, is an interesting area in the development of new drugs. For instance, several 1,4-dihydropyridines (1,4-DHPs) function as neuroprotectants, antianginal [1–3], anti-inflammatory [4], antitubercular [5], analgesic [6] and antithrombotic agents [1,7]. Pyridines could act as potent HIV protease inhibitor [1], and some derivatives are important building blocks for the construction of chemosensors [8].

Hantzsch reaction is one of the most broadly used method for 1,4-DHPs synthesis, and it involves condensation of a β -dicarbonyl compound, **1**, with an aldehyde, **2**, and a source of ammonia (ammonium acetate), **3**; the reaction is typically carried out in acetic acid medium or in refluxing alcohol [9], Fig. 1. It has been reported that asymmetric 2-phenylpyridines could be obtained as the main product, instead of the expected 1,4-DHPs, using the Hantzsch reaction at room temperature, under solvent and oxidant-free conditions and after 72 h of reaction [10].

Notwithstanding, not only temperature but also the presence of a catalyst may change product selectivity; furthermore, after the formation of the ester enamine, **4**, and the Knoevenagel condensation product, **5**, (Fig. 1) the reaction could follow the 1,4 addition through 1,4-dihydropyridine, **6**, with a subsequent oxidation to the corresponding pyridine, **8**, or the 1,2-addition to form the 1,2-dihydropyridine, **7**, with its oxidation to 2-phenylpyridine, **9** [11].

An adequate combination of temperature and acid-base properties of the catalyst has an important role in the selectivity of the Hantzsch reaction [10,11]. Catalytic systems based on MnO₂ and CeO₂, showed higher selectivity to the 2-phenylpyridine (over 91%) at 25 °C, but the selectivity changed when the temperature was increased to 80 °C, favoring the formation of the 1,4-DHP (75% of selectivity over CeO₂) but not the pyridine [11]. Unsupported iron nanoparticles of Fe₂O₃ have shown also activity in the synthesis of 1,4-DHPs (yields above 80%) at 90 °C [12].

The use of biomimetic catalysts of the cytochrome P-450 such as phthalocyanines is a topic of interest in the research field, due to the great versatility and reactivity of these molecules which depends on the metal center, the structural changes in the macrocycle, and the substituents present in the periphery, Fig. 2 [13,14]. The phthalocyanines (Pc) have been successfully used in several

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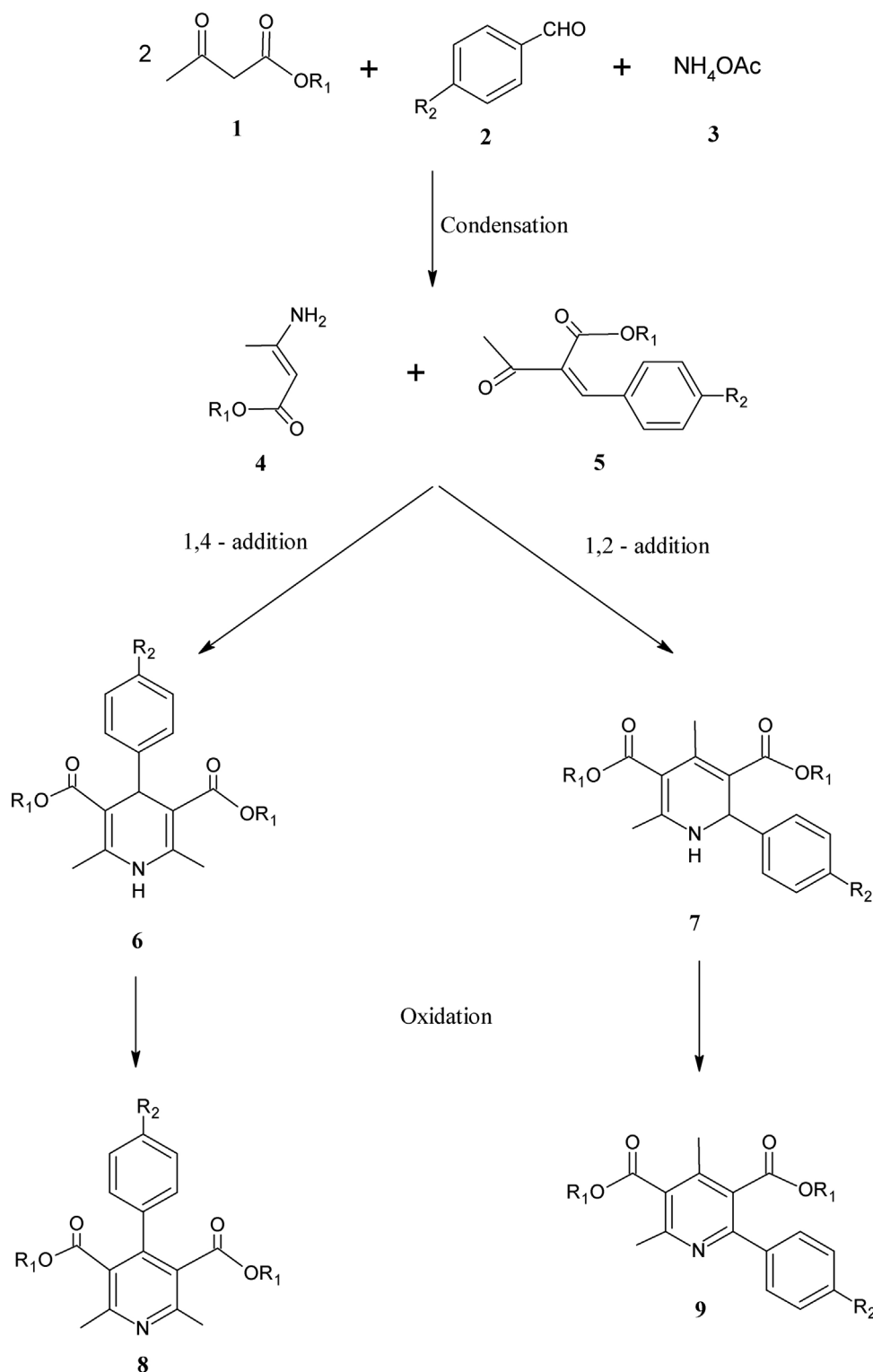


Fig. 1. Schematic representation of the synthesis of 1,4- and 1,2-phenylpyridines (compounds 6 and 7, respectively) and their corresponding oxidation products (compounds 8 and 9, respectively) over immobilized metallic phthalocyanines as catalysts.

reactions among them oxidations and reductions [14,15], amination and amidation of C–H bonds [16], aziridination of olefins [17], Biginelli condensation to 3,4-dihydropyridinones [18], and C–C coupling [19]. The Pc are very attractive as catalysts due to their low cost and straightforward preparation on a large scale as well as their chemical and thermal stability [20].

Moreover, activity and stability of phthalocyanines can be reached by ring substitution with electron-withdrawing groups, by introduction of a metal to their structure and by their immobilization [14,21,22]. When metal phthalocyanine complexes are immobilized on inorganic supports such as siliceous materials, not only is facilitated their recovery from the reaction media, but also lead to the presence of monomeric and μ -oxo dimeric species

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