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Silica-based nanocatalysts in the C—C and C-heteroatom bond forming cascade reactions for the synthesis of biologically active heterocyclic scaffolds

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"Our dear Dr. Elena Soriano will always remain in our memory; a scientist with strong convictions, great interest and passion for chemistry, which accompanied her until the last days."

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ABSTRACT

The design and development of hybrid materials with application in catalysis science is an interesting researching field, especially in the chemical industry for fine chemicals production. The properties of nanostructured catalysts can be changed by tuning the interaction between the support and the active phases. Silica nanoparticles are very convenient solid supports for the synthesis of organic-inorganic hybrid nanocatalysts, endowing them of the required features to optimize activity and selectivity, stability and recyclability. In this review, we analyze the latest developments and give a perspective concerning the recent applications of silica-based nanocatalysts for the synthesis of heterocyclic scaffolds, biologically active, *via* cascade reactions.

Heterocyclic rings often are the structural cores responsible of the biological activities in natural products and synthetic compounds. These systems are frequently synthesized by multicomponent reactions (MCRs), through cascade reactions. Such versatile catalytic systems have been successfully applied in a great variety of organic transformations for the synthesis of complex molecules and would play a key role in establishing new and more efficient sustainable technologies.

1. Introduction

Heterocyclic compounds have always attracted a great interest because of their pharmaceutical applications. Heterocyclic rings often are the structural cores responsible for the biological activities in natural products and synthetic compounds [1,2]. Heterocyclic scaffolds are frequently synthesized by multicomponent reactions (MCRs), through cascade reactions, in an efficient, selective, and safe manner emerging as a powerful and highly valuable strategy for the rapid synthesis of great molecular diversity [3]. In order to develop new and more sustainable methodologies for the green synthesis of especially relevant heterocycles, efforts of chemists and engineers on the design of more efficient and selective catalytic technologies, even in combination with the use of clean energy resources, are still required.

In the last decades, it has been produced an exponential growth in the application of inorganic solid nanocatalysts in organic synthesis allowing the upgrade and necessary renewal of chemical processes. These features offer environmental and sustainable solutions to the industrial sector involving a new scenario.

In other sense, silicon is one of the most abundant chemical element mainly as forming silicate minerals. Silica-based nanoparticles (NPs) have a great variety of applications; due to their biocompatibility properties, these materials can be applied on biomedicine as functionalized nanosystems for anti-cancer therapy [4], drug delivery technologies [5], development of biosensors [6] and also in the Light-Emitting Devices manufacture [7], among others applications. Silica-based materials with different structural and morphological characteristics and diverse compositions are also frequently used as versatile heterogeneous nanocatalysts, an important scientific field with high industrial repercussion [8]. In

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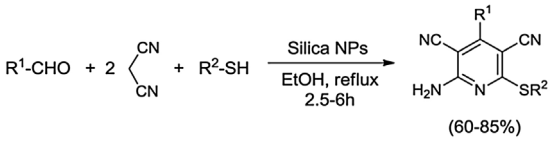


Scheme 1. Synthesis of highly substituted pyridines catalyzed by silica NPs.

general, silicas in all their forms show high chemical and thermal stability and tailored textural properties, which make them useful materials for catalytic applications. Although this type of materials is able to catalyze a few chemical processes by themselves as pure solids, their catalytic properties often have to be optimally tailored, thus acting as active phases or even as support of those. In this context, this work is aimed to present an overview related to the use of modified silica-based materials in the synthesis of biologically active heterocyclic scaffolds. This revision covers the most recent advances on the development of catalytic technologies involving functionalized silica NPs and periodic ordered mesoporous silicas (OMSs) for the heterocycles synthesis through cascade reactions.

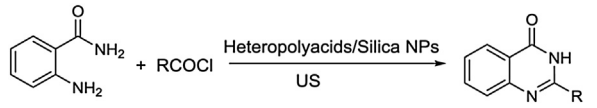
2. Silica nanoparticles

During the last decade, silica nanoparticles (NPs) have aroused great attention thanks to their exclusive physicochemical properties as well as the ability to control and adjust them. High surface area, firm framework, nanometer size, and very good thermal, mechanical and chemical stability are the particular properties of silica NPs [9]. These singular properties are responsible for its remarkable catalytic activity in a broad range of organic transformations. In addition, the silanol groups present on their surface enable the incorporation of a wide range of functionalities and the immobilization of heteropolyacids and metal complexes among others. It seems that molecular interactions between silica functional groups and metal species are key in the formation of highly active catalytic centers. Moreover, silica NPs as catalyst and catalytic support are neutral, very mild, inexpensive, reusable and ecofriendly, which makes them a very competitive material in heterogeneous catalysis.

2.1. SiO_2 as catalysts and catalyst support

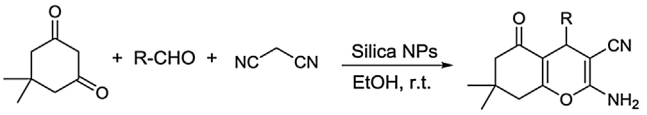
The so-called *privileged medicinal scaffolds* are a platform for the synthesis of pharmaceutical agents with numerous applications since they provide ligands of different biological receptors, as mentioned. Substituted pyridines are a type of privileged scaffolds with diverse pharmacological activities. In this context, *Banerjee et al.* [10] carried out the multicomponent reaction of aliphatic and aromatic aldehydes, malononitrile and thiols over silica NPs to obtain substituted pyridines, and in particular 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines (Scheme 1). The authors observed that OH groups on silica NPs surface are responsible for their catalytic activity. The optimization of different reaction parameters led to improved yield values (85% yield, 2.5 h, EtOH/reflux, 50 nm silica NPs).

Heravi et al. [11] immobilized Preyssler heteropolyacids of type $H_{14}[NaP_5W_{30}O_{110}]$ into NPs and studied their catalytic behavior in the synthesis of 4(3*H*)-quinazolinone derivatives from reaction of 2-amino-benzamide and acyl chlorides under ultrasound activation (Scheme 2). The authors demonstrated that silica-supported Preyssler NPs led to improved yields than Preyssler one. The particular features of this proposal were the achievements of high yields, short reaction times compared with those required under reflux conditions, the possibility of reuse the catalyst and simple work up procedure.



Scheme 2. Synthesis of 4(3*H*)-quinazolinone derivatives catalyzed by $H_{14}[NaP_5W_{30}O_{110}]$/silica NPs.

Scheme 3. Synthesis of isoindolinine derivatives catalyzed by silica NPs.



Scheme 4. Synthesis of tetrahydrobenzo[*b*]pyran derivatives catalyzed by silica NPs.

Ramazani et al. [12] studied an efficient procedure for the one-pot synthesis of 2,3-dihydro-1*H*-isoindolone derivatives *via* multicomponent reaction of 6-formyl-2,3-dimethoxybenzoic acid, secondary amines and alkyl isocyanides over silica NPs, at room temperature, in absence of any solvent (Scheme 3). The optimum amount of the catalyst was 0.2 g, affording excellent yields (94%, 7 h). These results were also compared with those obtained using silica gel powder as catalyst (48%, 24 h).

Banerjee et al. [13] synthesized 4*H*-pyran derivatives, with biological and pharmacological activity, *via* one-pot multicomponent reaction of an aldehyde, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione or ethyl acetoacetate over silica NPs catalysts (Scheme 4). They also carried out the synthesis of polysubstituted aniline derivatives *via* the reaction of an aldehyde, malononitrile and a ketone using silica NPs catalysts. The results showed that silica NPs are very effective catalysts to synthesize both 4*H*-pyran derivatives (up to 98% yields in only 30 min) and polysubstituted aniline derivatives (up to 65% yields in 2 h). Moreover, the reuse of the silica NPs catalyst displayed that the loss of activity was minimal after eight runs.

Rafiee et al. [14,15] synthesized nano silica powders from rice husk ash (RHA) that is an abundant agricultural waste. The authors prepared silica NPs supported $H_3PW_{12}O_{40}$ (PW) (PW/N-SiO_2) and silica NPs supported $H_5CoW_{12}O_{40}$ (CoW/N-SiO_2) catalysts. These catalysts were tested successfully in the solvent-free benzylation reaction of cyclic and acyclic 1,3-dicarbonyl compounds with benzylic alcohols, Mannich reaction, Claisen-Schmidt condensation and Biginelly reaction *via* reaction of acetylacetone, benzaldehyde with urea, and Hantzsch reaction *via* reaction of benzaldehyde, ethyl acetoacetate and amine [16]. Table 1 summarizes some of the results obtained in the catalytic activity study of PW/N-SiO_2, compared to those of the nano silica powders.

It is noteworthy to mention that in the case of CoW/N-SiO_2 catalysts the characterization results showed a very good distribution of their acid sites and a higher number of them compared to the catalyst prepared from commercial silica (CoW/SiO_2), or the bulk CoW. It appears that CoW/N-SiO_2 catalyst possesses bifunctional properties, such as Brønsted acidity and electron transfer capacity, being able to catalyze the reaction following two different routes.

Samani et al. [17] also supported tungstophosphoric acid on NPs to prepare efficient catalyst in the thermally activated synthesis of azlactone derivatives *via* reaction of aldehydes with hippuric acid in

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