


Nickel-Catalyzed, One-Pot Synthesis of Pyrazoles [†]

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Abstract: Recently, multi-component, one-pot reactions have been shown to be efficient and environmentally friendly methods compared to traditional, linear-step syntheses. Heterogeneous catalyzed multicomponent reactions are one of the green approaches to the synthesis of organic compounds, especially pyrazoles and their derivatives. Here we demonstrate the one-pot synthesis of pyrazoles using heterogeneous nickel-based catalysts for the condensation of various hydrazine, ketone derivatives, and aldehyde derivatives at room temperature. The thus synthesized heterogeneous catalyst can be reused up to the seventh cycle without much loss of catalytic activity.

Keywords: pyrazoles; heterocycles; multicomponent synthesis; organic synthesis; heterogeneous catalysis



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1. Introduction

Nitrogen-containing heterocycles are key core structures that underlie many natural products, pharmaceuticals, and agrochemicals [1–7]. Among them, the pyrazole moiety is an extremely important synthetic unit in the pharmaceutical industry [8,9], has abundant and potent biological activities such as antipyretic [10], antibacterial [11], and insecticidal [12].

Pyrazole moieties are widely used in bioactive molecules (Figure 1) [13] and functional materials [14–18]. To date, various methods for the construction of pyrazole rings are available [19–24], such as the classical Knorr pyrazole synthesis of 1,3-diketones and TsNHNH₂, Refs [25–27] via direct hydrazination of propargyl alcohols. A two-step synthesis and subsequent intramolecular cyclization of propargyl hydrazides, cycloaddition of [28–30] [3+2] terminal alkynes to hydrazones, and aldehydes/ketones generated in situ to diazo compounds [31–33]. Today, as a privileged structure, it can be synthesized by the reaction of 1,3-dipolar cycloaddition of diazo compounds [34], acetylenone, [35] N-sulfonylhydrazones, [36] or chalcone [37], and hydrazine [38]. In this regard, various catalysts have been investigated to catalyze the formation of pyrazoles: Cao and his colleagues used Zn complex [39]; El-Remaily and his group used thiazole complexes under ultrasonic reaction conditions [40]; Amirnejat et al. [41] used Superparamagnetic Fe₃O₄@Alginate supported L-arginine; and recently, nano SiO₂ was used by Abou Elmaaty and his group [42].

In the present work, we have described a new, efficient, and environmentally benign synthetic method for the formation of pyrazoles using hydrazine, aldehyde, and ketone through a one-pot method in the presence of a Nickel-based heterogeneous catalyst at room temperature.

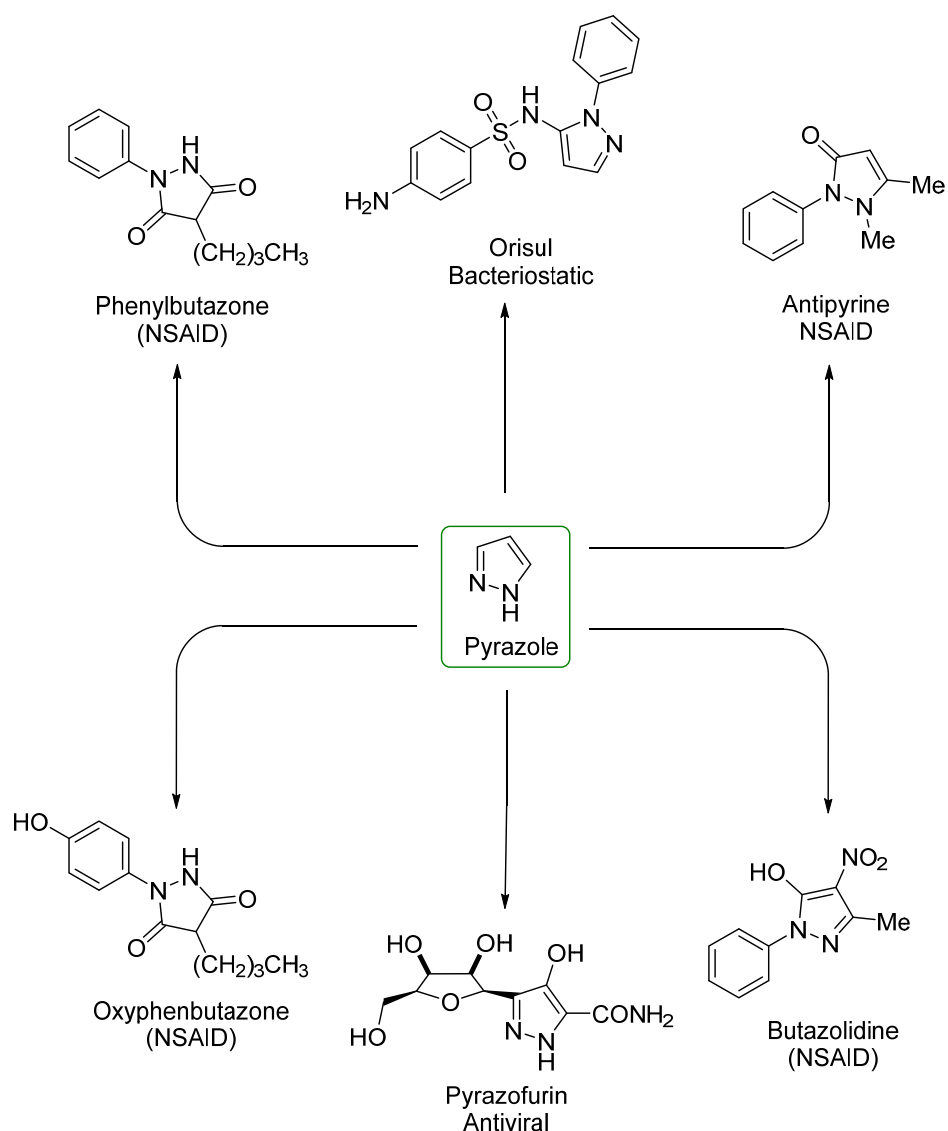


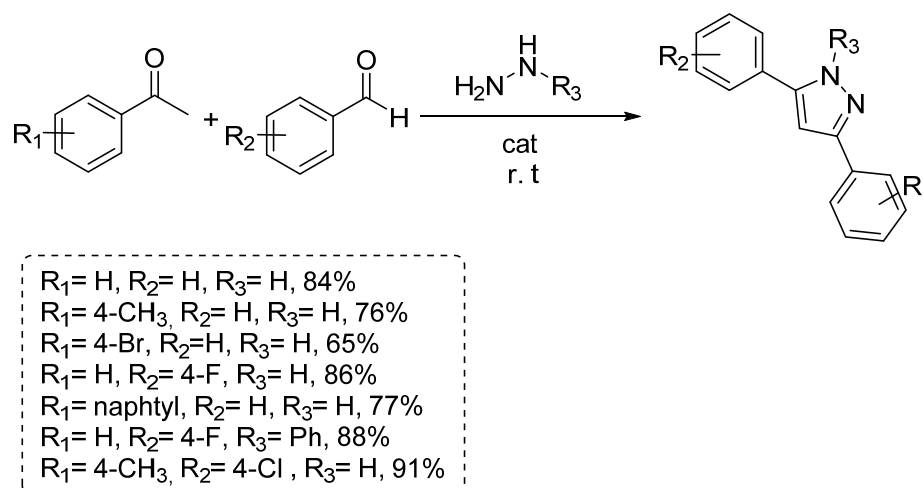
Figure 1. Examples of biologically active Pyrazole derivatives.

2. General Experimental Procedure

The synthesis of Pyrazole derivatives in the presence of Nickel-based heterogeneous catalysis was effected using the already reported approach [43]. Initially, acetophenone (0.1 mol) and hydrazine (0.1 mol) and a solid Nickel-based heterogeneous catalyst (10 mol%) were charged into a round bottom flask containing Ethanol (10 mL). After stirring for 30 min, benzaldehyde was added dropwise to the reaction mixture, and it was stirred for 3 h at room temperature. After completion of the reaction as monitored by TLC, the desired pyrazoles were washed with water and toluene to remove the unreacted materials and recrystallized by methanol or purified by column chromatography.

3. Results

The optimization of the reaction conditions was carried out through testing using different solvents at different temperatures and different catalyst loadings. When optimized conditions were in hand, the reaction was generalized to different derivatives of acetophenones and benzaldehydes. Different Pyrazole derivatives were obtained in the presence of a heterogeneous Nickel-based catalyst in good to excellent yields (Scheme 1).



Scheme 1. One-pot synthesis of Pyrazoles in the presence of Nickel-based heterogeneous catalyst.

4. Conclusions

In conclusion, in this work, we report the synthesis of pyrazoles using hydrazine, various acetophenone derivatives, and various aldehydes in the presence of heterogeneous nickel-based catalysts. The reaction proceeds with low catalyst loading and a short reaction time, which is an economical and environmentally friendly method.

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