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Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium

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Abstract—An expeditious room temperature synthesis of pyrazoles and diazepines by condensation of hydrazines/hydrazides and diamines with various 1,3-diketones is described. This greener protocol was catalyzed by polystyrene supported sulfonic acid (PSSA) and proceeded efficiently in water in the absence of any organic solvent within 1–2 min.

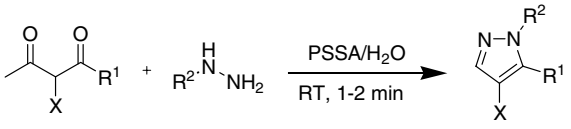
1. Introduction

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds,[1] including blockbuster drugs such as Celebrex[2] and Viagra.[3] They also possess important biological properties such as antitumor cyclin-dependent kinase (CDK) inhibitors,[4] monoamine oxidase-B (MAO-B) inhibitors, and antiinflammatory agents.[5] Recently, they have also emerged as potential atypical antipsychotics.[6]

Several syntheses of pyrazoles have been developed and by far the most prevalent method of choice is the reaction of 1,3-diketones with hydrazines.[7] Other methods for the synthesis of pyrazoles that do not require 1,3-diketones have been reported.[8] Recently, a few efficient methods have been developed,[9] however, most of these utilize a circuitous route, require longer reaction time, and are often carried out in organic solvents. Compared with the reactions in organic solvents, solventless reactions are often rapid, regio- or chemoselective, occur in high yields and have environmental and economic advantages.[10,11]

In our continued quest for greener synthetic pathways,[12] herein, we report an expeditious synthesis of pyrazoles by the reaction of 1,3-diketones with hydrazines and hydrazides catalyzed by polystyrene supported sulfonic acid (PSSA), which proceeded efficiently in water in the absence of any organic solvent at room temperature within 1–2 min (Scheme 1).

To optimize the reaction conditions, we studied the condensation of pentane-2,4-dione with phenyl hydrazine, using various acid catalysts: acetic acid, *p*-toluene sulfonic acid, and PSSA. Although reaction proceeds in each case, the yield and the rate of reaction is superior in the case of PSSA as compared to other catalyst. The general efficiency of this protocol was then studied for the synthesis of a variety of pyrazoles and the results are summarized in Table 1.



R^1 = Me, OEt
R^2 = Ph, 4-ClPh, COPh
CO-furyl, CO-thienyl
X = H, Et, Cl

Scheme 1. PSSA catalyzed pyrazole synthesis in water.

Keywords: Pyrazoles; Diazepines; Polystyrenesulfonic acid (PSSA), Aqueous medium.
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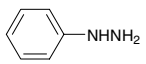
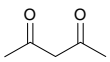
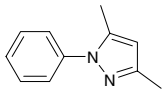
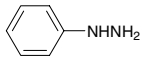
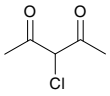
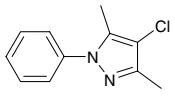
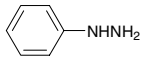
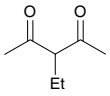
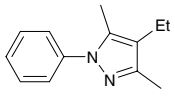
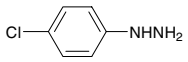
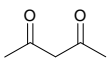
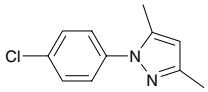
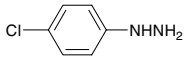
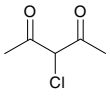
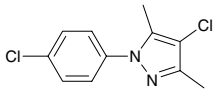
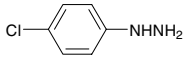
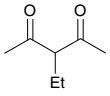
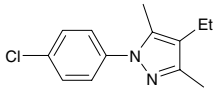
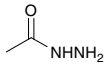
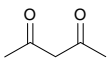
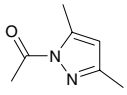
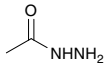
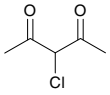
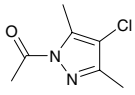
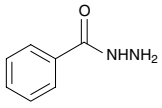
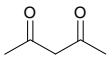
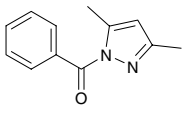
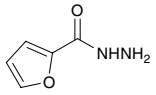
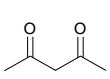
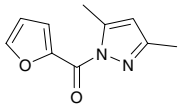
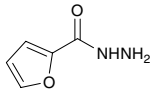
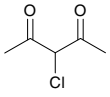
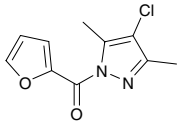
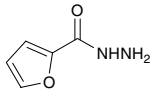
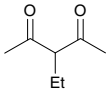
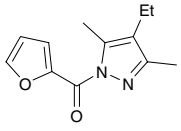
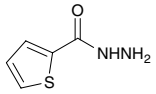
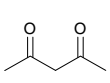
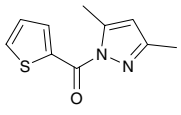
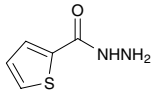
Table 1. PSSA catalyzed synthesis of pyrazoles at room temperature in aqueous medium[a]

Entry	Hydrazine/hydrazide	Diketone	Product	Yield[b] (%)
1				92
2				75
3				82
4				85
5				72
6				80
7				90
8				78
9				90
10				92
11				85
12				88
13				91
14				85