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Mixing with microwaves: solvent-free and catalyst-free synthesis of pyrazoles and diazepines

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ABSTRACT

A simple and facile condensation of hydrazines/hydrazides and diamines with 1,3-diketones/β-ketoester leads to the preparation of pyrazoles and diazepines in high yields. This eco-friendly protocol is accelerated by microwave heating and efficiently carried out without any reaction solvent or catalyst in as little as 5 min.

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1. Introduction

Pyrazole derivatives are important biologically active compounds. They are significant in the agrochemical and pharmaceutical industry. In medicinal chemistry, they are known for their antitumor activity,[1] angiotensin converting enzyme inhibitor activity,[2] antimicrobial activity,[3] anti-inflammatory activity,[4] antiviral activity,[5] and anticonvulsant and antidepressant activities.[6] Celecoxib, a pyrazole derivative, is used successfully as an analgesic in arthritis.[7]

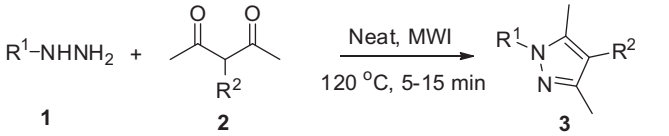
The synthesis of pyrazoles can be achieved by several different routes.[8–13] The path involving 1,3-diketones and aryl hydrazines is one of the prominent methods for the preparation of substituted pyrazoles. The earlier reported reaction protocols include the use of various acidic catalysts, such as hydrochloric acid,[14] sulfuric acid,[15] and phosphotungstic acid[16] in solvents namely ethanol and water. More recently, our room temperature synthesis of these molecules has been accomplished using polystyrene sulfonic acid in water[17] or using glutathione supported magnetic nanoparticles.[18]

The synthesis of these molecules is now achieved under solvent-free and catalyst-free conditions to develop a greener and useful protocol; the reactions under solvent-free conditions are known to be rapid and chemo- or regioselective, resulting in high yields of products that have both environmental and economic advantages.[19]

2. Results and discussion

In our efforts to develop greener and more facile organic transformations, we have focused on the synthesis of pyrazoles under solvent-free and catalyst-free conditions. Microwave (MW) irradiation of a neat mixture of aryl hydrazines and 3-substituted-pentane-2,4-diones resulted in the formation of pyrazoles in high yields.

Initially, a neat mixture of phenyl hydrazine and pentane-2,4-dione was ground via mortar and pestle at ambient temperature, resulting in almost 40% conversion to the pyrazole product. The mixture was subsequently heated in an oven at 80 °C for 30 min to improve the conversion to 70%. In order to expedite the reaction, a fresh equimolar mixture of the reactants was subjected to MW irradiation at 100 °C for 5 min, affording complete conversion to the desired product. The neat conversion to the product, as evidenced by the gas chromatography, avoided the need for further work-up.



1 2 3

R^1 = Ar, ArCO-
R^2 = H, Cl, Et

Scheme 1. Solvent-free and catalyst-free synthesis of pyrazoles **3**.

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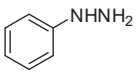
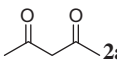
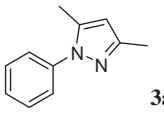
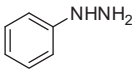
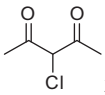
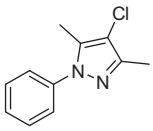
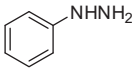
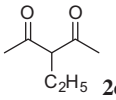
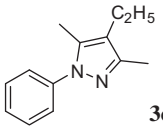
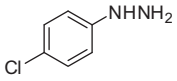
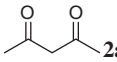
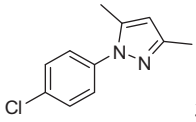
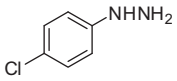
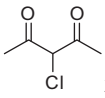
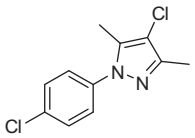
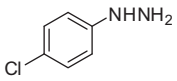
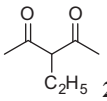
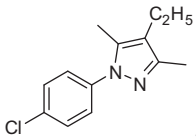
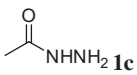
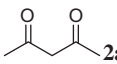
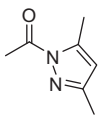
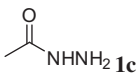
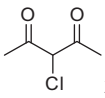
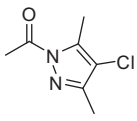
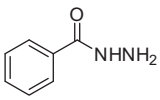
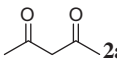
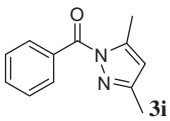
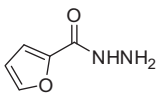
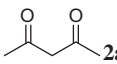
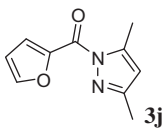
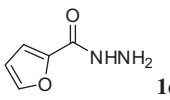
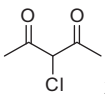
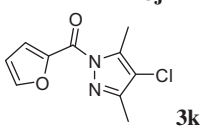
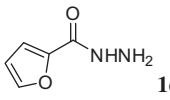
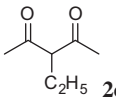
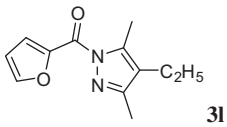
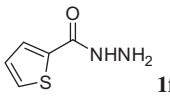
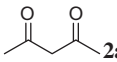
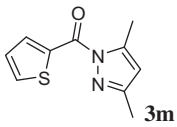
Table 1
Microwave-assisted neat synthesis of pyrazoles **3**[a]

Entry	Hydrazine/Hydrazide **1**	Diketone **2**	Product **3**[b]	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	5	99
2	 **1a**	 **2b**	 **3b**	5	98
3	 **1a**	 **2c**	 **3c**	10	95.
4	 **1b**	 **2a**	 **3d**	10	98
5	 **1b**	 **2b**	 **3e**	10	97
6	 **1b**	 **2c**	 **3f**	15	98
7	 **1c**	 **2a**	 **3g**	10	98
8	 **1c**	 **2b**	 **3h**	6	98
9	 **1d**	 **2a**	 **3i**	30	98
10	 **1e**	 **2a**	 **3j**	10	99
11	 **1e**	 **2b**	 **3k**	10	98
12	 **1e**	 **2c**	 **3l**	15	97
13	 **1f**	 **2a**	 **3m**	10	98

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