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Greener and rapid access to bio-active heterocycles: one-pot solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles

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Abstract

A novel one-pot solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles by condensation of acid hydrazide and triethyl orthoalkanates under microwave irradiations is reported. This green protocol was catalyzed efficiently by solid supported Nafion®NR50 and phosphorus pentasulfide in alumina (P_4S_{10}/Al_2O_3) with excellent yields.

Keywords: 1,3,4-Oxadiazole; 1,3,4-Thiadiazole; Nafion; P_4S_{10}/Al_2O_3; Solvent-free reaction; Microwave irradiation

1,3,4-Oxadiazoles and 1,3,4-thiadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive.[1–5] The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocycles. These molecules are also utilized as pharmacophores due to their favorable metabolic profile and ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents such as tiodazosin[6] and nesapidil[7] as well as antibiotics such as furamizole[8] contain the oxadiazole nucleus. They are also useful as HIV integrase inhibitors and the angiogenesis inhibitors.[8,9]

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles.[10–19] Most of these protocols are multi-step in nature, and generally involve the cyclization of acid hydrazides with a variety of reagents, such as thionyl chloride, phosphorus oxychloride or sulfuric acid, usually under harsh reaction conditions. Recently, a few efficient examples have been reported for the synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides. However, these protocols use expensive catalysts, and require longer times for the completion of the reactions.[20]

Ainsworth in 1954 reported a one-step synthesis of these 1,3,4-oxadiazoles from corresponding acid hydrazides.[21] However, despite its common use, this protocol suffers from harsh conditions, such as use of excess orthoformates and longer reaction time. In view of the emerging interest in sustainable chemistry,[22] and in keeping with our emphasis on the development of green synthetic methods,[23] we revisited this Ainsworth protocol and herein report Nafion catalyzed synthesis of 1,3,4-oxadiazoles under microwave (MW) irradiation (Scheme 1).

After screening a range of usual inorganic and organic acids and exploring the scope of various solvents, we found that the solid supported Nafion®NR50[24] was the most efficient catalyst for this protocol in the absence of any solvent.[25] The efficiency of this protocol was then studied for the synthesis of various 1,3,4-oxadiazoles and the results are summarized in Table 1.

Various hydrazides reacted efficiently with triethyl orthoformate, triethyl orthoproponate and triethyl orthobenzoate to afford the desired 1,3,4-oxadiazoles in good

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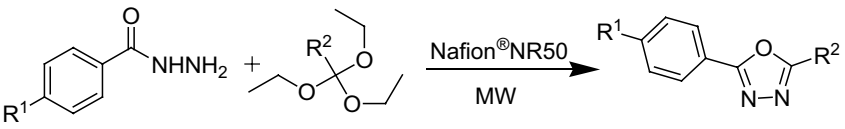
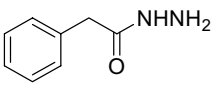
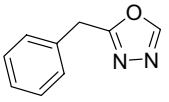
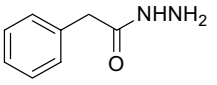
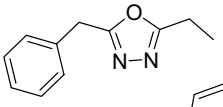
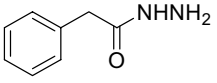
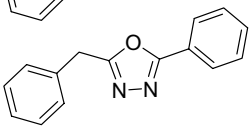
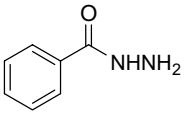
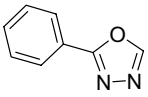
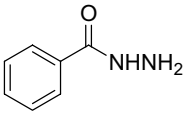
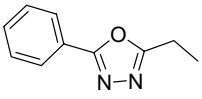
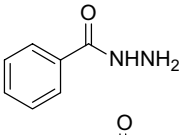
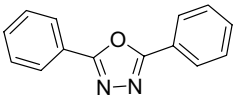
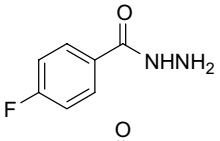
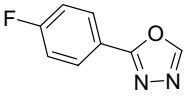
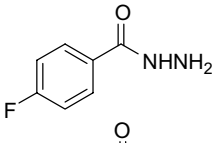
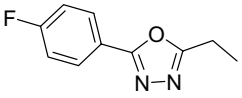
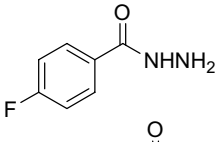
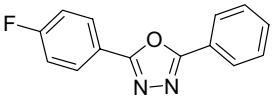
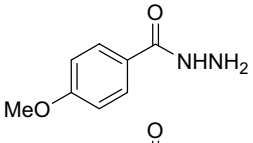
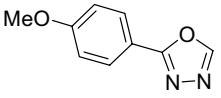
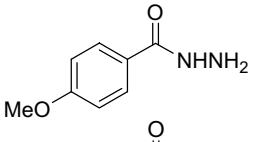
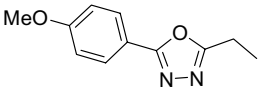
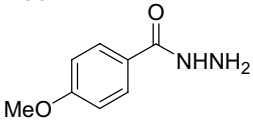
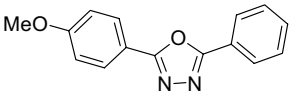


R^1 = H, F, OMe, 2-furyl, 2-thienyl, 4-pyridyl
R^2 = H, Et, Ph

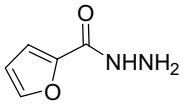
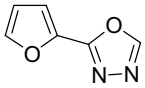
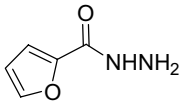
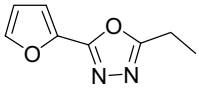
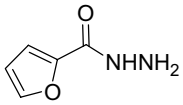
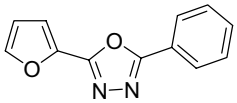
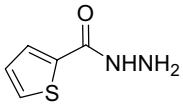
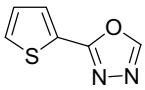
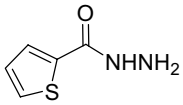
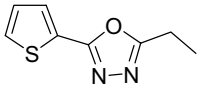
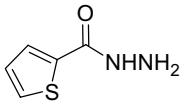
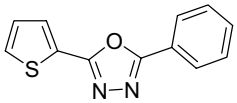
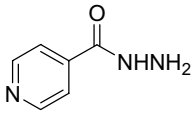
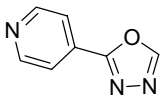
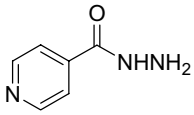
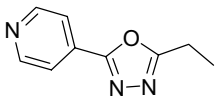
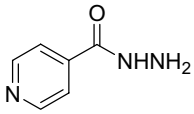
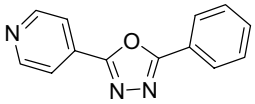
Scheme 1. Nafion catalyzed 1,3,4-oxadiazoles synthesis.

Table 1
Nafion®NR50-catalyzed synthesis of 1,3,4-oxadiazoles under MW irradiation[a]

Entry	Hydrazide	Product	Yield (%)
1			80
2			80
3			81
4			85
5			88
6			88
7			90
8			90
9			90
10			90
11			90
12			90

[a] Reaction temperature 80 °C, time 10 min, and no solvent.

Table 2
Nafion®NR50-catalyzed 1,3,4-oxadiazoles synthesis using heterocyclic hydrazides[a]

Entry	Hydrazide	Product	Yield (%)
1			68
2			70
3			72
4			78
5			78
6			80
7			78
8			80
9			80

[a] Reaction temperature 130 °C, time 25 min, and no solvent.

yields (entries 1–12). This approach establishes a convenient and flexible method for the synthesis of 1,3,4-oxadiazoles having functional arms at the 2 and 5 positions, which can be further elaborated. The reactions also proceed without catalyst, but require higher temperature (135 °C) with longer reaction time (1.5 h) under MW irradiation. This reaction also gets completed under conventional heating in an oil bath at the reflux temperature but requires an extended period of time, 16–18 h.

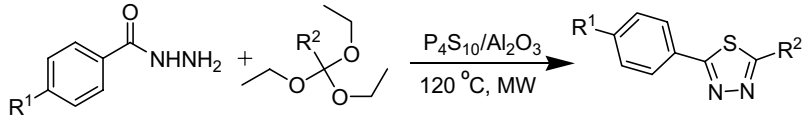
It is noteworthy to mention that these reactions proceeded efficiently without any solvent, even though they involved the use of heterogeneous solid supported catalyst. This is due to selective absorption of microwaves by reactants, polar intermediates and Nafion, which accelerate the reaction rate.[26] Also the catalyst Nafion®NR50 is very easy to handle, as it involves simply the addition of Nafion bead (like a glass bead) in a reaction vessel, which can be physically removed by forceps after the completion of reaction.

In view of the exceptional biological properties of heterocyclic hydrazides and to further define the scope of this reaction, a wide variety of heterocyclic hydrazides were evaluated for this cyclization reaction and the results are summarized in Table 2. Various heterocyclic hydrazides such as 2-furyl hydrazides (entries 1–3), 2-thiophenyl hydrazides (entries 4–6), and 4-pyridyl hydrazides (entries 7–9) reacted efficiently to afford corresponding 1,3,4-oxadiazoles in good yields.

Finally, this protocol was also extended for one-step synthesis of 1,3,4-thiadiazoles from acid hydrazides. One of us has previously used phosphorus pentasulfide in alumina (P_4S_{10}/Al_2O_3) as an efficient thionating agent for various carbonyl compounds.[27] We used this reagent for one-pot synthesis of 1,3,4-thiadiazoles under MW irradiation conditions (Scheme 2) and to the best of our knowledge this is the first report on one-step one-pot synthesis of 1,3,4-thiadiazoles from acid hydrazides.

Using the optimized reaction conditions,[25] the efficiency of this protocol was studied for the synthesis of various thiadiazoles. The results are summarized in Table 3. Various aromatic and heterocyclic hydrazides reacted efficiently with P_4S_{10}/Al_2O_3 to yield thiadiazoles in a single step. The reaction proceeds efficiently without any solvent, with moderate to good yields of 1,3,4-thiadiazole.

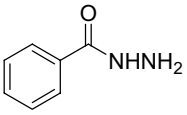
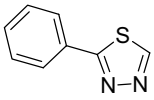
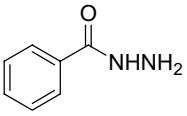
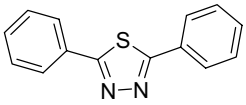
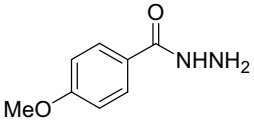
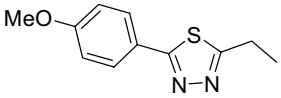
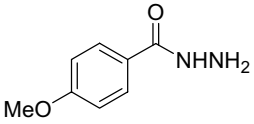
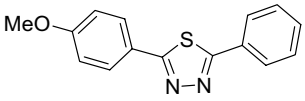
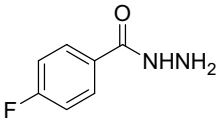
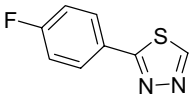
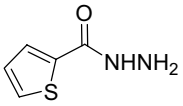
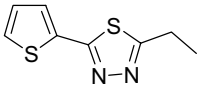
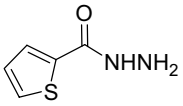
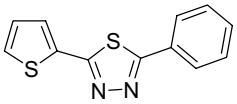
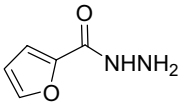
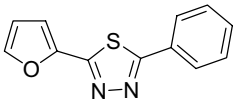
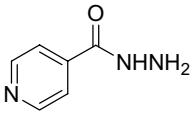
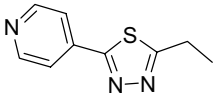
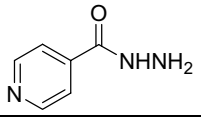
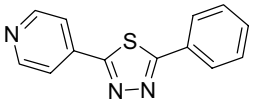
For practical applications of the catalyst Nafion®NR50, the lifetime of the catalyst and its level of reusability are important factors. The catalyst showed excellent recyclability in the synthesis of 1,3,4-oxadiazoles from benzoic hydrazide and triethylorthoformate. The reactions were carried out under similar conditions (80 °C/10 min) without any solvent. After the completion of the first reaction to afford the corresponding 1,3,4-oxadiazoles in 85% yield, the catalyst was recovered by forceps, washed with dichloromethane, dried and a new reaction was then performed with fresh reactants under the same conditions; Nafion®NR50 could be used for at least five times without any change in activity.



R^1 = H, F, OMe, 2-furyl, 2-thienyl, 4-pyridyl
R^2 = H, Et, Ph

Scheme 2. P_4S_{10}/Al_2O_3 mediated synthesis of 1,3,4-thiadiazoles.

Table 3
P_4S_{10}/Al_2O_3 mediated synthesis of 1,3,4-thiadiazoles[a]

Entry	Hydrazide	Product	Yield (%)
1			65
2			70
3			70
4			70
5			65
6			70
7			72
8			68
9			70
10			70

[a] Reaction temperature 120 °C, time 10 min, and no solvent.

In conclusion, we have demonstrated a new and efficient approach for the synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles, which may find useful application in drug discovery. Also the use of solid supported, relatively low toxic, and inexpensive Nafion®NR50 and P_4S_{10}/Al_2O_3 as a catalyst and the solvent-free reaction conditions are additional eco-friendly attributes of this synthetic protocol.

Acknowledgment

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25. *Experimental procedure for the synthesis of 2-phenyl-1, 3, 4-oxadiazole*: Phenyl hydrazide (0.13 g, 1 mmol) and triethylorthoformate (0.17 g, 1.2 mmol) were placed in 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. To this, 20 mg (in general one small bead) of catalyst Nafion®NR50 was added and the reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 80 ± 5 °C (temperature monitored by a built-in infrared sensor), power 40–140 W, and pressure 20–40 psi for 10 min. After completion of the reaction, the solid catalyst was physically removed by forceps, to isolate crude 1,3,4-oxadiazoles, which were further purified by column chromatography, 85% yield. ^{1}H NMR ($CDCl_3$): δ 8.5 (s, 1H), 8.1 (m, 2H), 7.5 (d, 3H); ^{13}C NMR ($CDCl_3$): δ 164, 152, 133, 129, 127, 123; MS: 146 (M^+), 118, 105, 90, 77, 63, 51.
For the synthesis of oxadiazole from heterocyclic hydrazide, the reaction conditions were, temperature, 130 °C; reaction time – 25 min; and Nafion®NR50 – 40 mg.
Typical experimental procedure for thiadiazole synthesis: The acid hydrazides (1 mmol), triethylorthoformate or triethylorthopropionate or triethylorthobenzoate (1.1 mmol) and 0.2 g of P_4S_{10}/Al_2O_3 were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer and the experimental procedure described above was followed, at temperature, 120 °C.
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