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A simple and efficient one step synthesis of 1,3,4-oxadiazoles utilizing polymer-supported reagents and microwave heating

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Abstract—1,3,4-Oxadiazoles can be rapidly and efficiently synthesized from a variety of carboxylic acids and acid hydrazides in one simple step. The use of commercially available PS-PPh_3 resin combined with microwave heating delivered the product 1,3,4-oxadiazoles in high yields and purities.

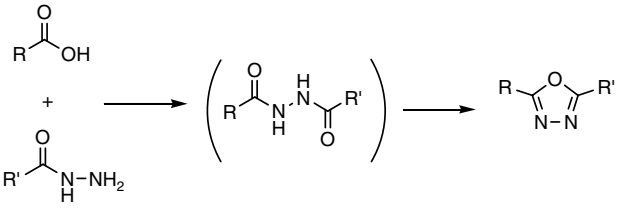
Polymer-assisted solution-phase (PASP) synthesis, which uses either polymeric reagents or scavenger resins, has received considerable interest over the past few years.[1] It provides a convenient method of performing chemical transformations with minimal workup, which is especially desirable in a high-throughput organic synthesis environment.

Microwave accelerated synthesis is also emerging as a powerful tool for high-throughput organic synthesis.[2] It has been demonstrated that the use of microwave heating can dramatically shorten reaction times, increase product purities and yields, and allow precise control of reaction parameters.

As part of our ongoing program to develop efficient and robust methods for the preparation of biologically relevant compounds from readily available building blocks, we sought to develop a convenient preparation of 1,3,4-oxadiazoles. 1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides. They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, anti-fungal, anti-inflammatory, and antihypertensive.[3]

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles.[4] These protocols are routinely multi-step in nature. The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorous oxychloride, and sulfuric acid, usually under harsh reaction conditions. Few reliable and operationally facile examples have been reported for the one step synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides (Scheme 1).[5]

Our initial studies proceeded by reacting carboxylic acids and acid hydrazides in the presence of various coupling reagents, such as PS-DCC and TBTU, under microwave heating conditions, none of which gave satisfactory yields of the desired 1,3,4-oxadiazoles. In many cases, the corresponding diacyl hydrazide was the major product obtained. It has been reported that in the presence of DMC (2-chloro-1,3-dimethylimidazolinium chloride), 1,3,4-oxadiazoles can be obtained in good yields from carboxylic acids and acid hydrazides in CH_2Cl_2 at ambient temperature.[6] In our hands, however, when DMC was added to a solution of carboxylic



Scheme 1. Synthesis of 1,3,4-oxadiazole from carboxylic acids and acid hydrazides.

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acid **1** and benzoic hydrazide **2** in CH_2Cl_2 at room temperature, only diacyl hydrazide **3** was formed (Scheme 2). Conversion to the 1,3,4-oxadiazole **4** was only observed when the reaction was heated under microwave conditions as shown in Scheme 2. It was found that when THF or CH_2Cl_2 was used as the solvent, the conversion of diacyl hydrazide **3** to 1,3,4-oxadiazole **4** was not complete and both **3** and **4** were observed in the crude LC/MS. However, when DMA was used as the solvent, a very good conversion to the desired 1,3,4-oxadiazole **4** (>90%) was obtained. The best result was achieved when CH_3CN was used as the solvent. Quantitative conversion to 1,3,4-oxadiazole **4** was observed when the reaction mixture was heated in the microwave at 150 °C for 20 min (Scheme 2). For optimal yields, it was found to be important to use 2 equiv of DMC in the reaction. With 1 equiv of DMC, only partial conversion to **4** was observed. Among the bases studied, PS-BEMP was shown to give the best yields of **4**.

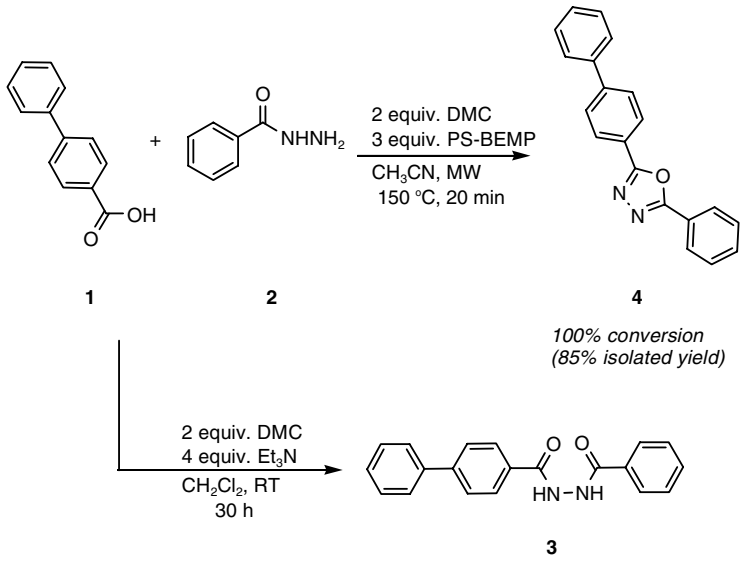
Although we were able to secure the desired 1,3,4-oxadiazole in the presence of DMC by microwave heating, the conversions were not satisfactory in some cases with other substrates (Table 1, entries 2 and 4). Moreover, since 2 equiv of DMC was needed to get the optimal yields of the desired 1,3,4-oxadiazoles, separation of the byproduct 1,3-dimethyl-2-imidazolidinone (DMI) was found to be non-facile. Although DMI can be washed away with water, the process was found to be unsuitable for operating in an automated format for library production.

Recently, we have reported an efficient one-pot synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes using either HBTU/PS-BEMP as the coupling reagent or PS-PPh_3/CCl_3CN via the in situ formation of acid chlorides.[7] It was thought that we might also be able to synthesize 1,3,4-oxadiazoles using analogous procedures. In practice, when carboxylic acid **1** and benzoic hydrazide **2** were heated together under microwave conditions in the presence of HBTU/PS-BEMP in CH_3CN (Scheme 3), the reaction was not clean as observed from the crude LC/MS. Diacyl hydrazide **3** was again found to be the major product obtained along with a small amount of the desired cyclized 1,3,4-oxadiazole **4** and other unidentified side products as determined from crude LC/MS and ^1H NMR. All attempts to improve the conversion to **4** by this method failed.

Our previous studies had shown that better yields of 1,2,4-oxadiazoles were often obtained with PS-PPh_3/CCl_3CN compared to the method using HBTU/PS-BEMP. However, under our original reaction conditions developed for 1,2,4-oxadiazoles, diacyl hydrazide **3** was obtained as the sole product in the presence of PS-PPh_3/CCl_3CN in THF (Scheme 3).

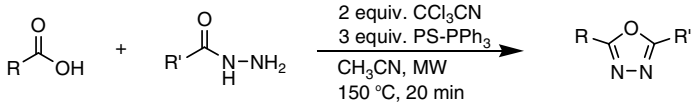
Compound **3** was subjected to a variety of different reaction conditions in search of a mild and efficient method to convert it to the corresponding 1,3,4-oxadiazole **4**. Encouragingly, we quickly discovered that **3** underwent smooth cyclization to the desired 1,3,4-oxadiazole **4** in quantitative yield in acetonitrile under microwave heating with 1 equiv CCl_3CN and 3 equiv PS-PPh_3 (Scheme 4).[8] In contrast, no cyclization product was observed when THF was used as solvent under the same condition. Thus, the choice of solvent has a dramatic effect on the second cyclization step. Unsatisfactory conversions were achieved using a variety of literature methods.[4c,f] The reaction worked equally well with or without an added base, such as DIEA. Here, the PPh_3/CCl_3CN reagent combination appeared to play a dual role in the conversion of carboxylic acid to acyl chloride in the first step and in the subsequent cyclization of the diacyl hydrazide to the 1,3,4-oxadiazole in the second step.

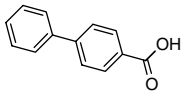
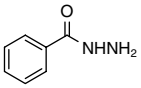
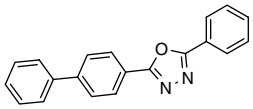
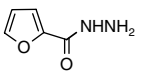
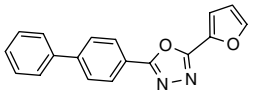
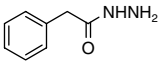
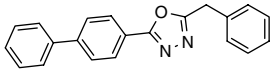
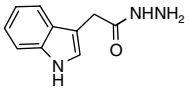
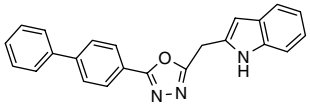
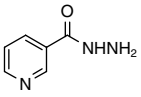
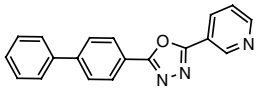
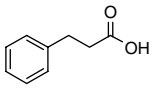
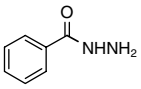
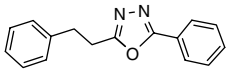
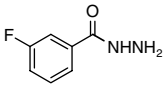
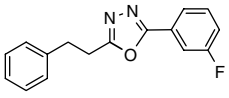
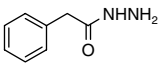
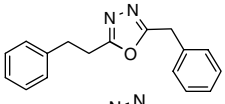
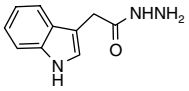
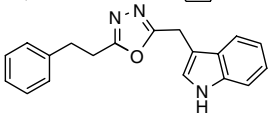
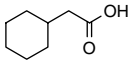
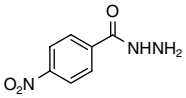
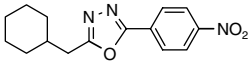
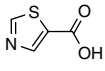
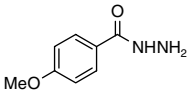
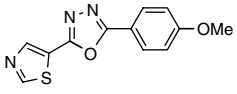
Gratifyingly, we were delighted to discover that these two steps could be efficiently carried out in one step in



Scheme 2. Synthesis of 1,3,4-oxadiazole **4** utilizing DMC.

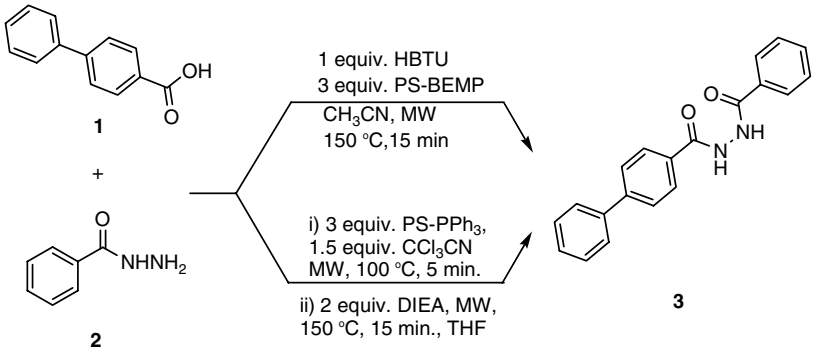
Table 1. Synthesis of 1,3,4-oxadiazoles from carboxylic acids and acid hydrazides with PS-PPh_3/CCl_3CN



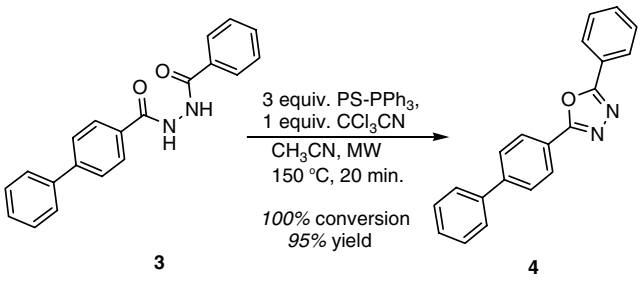
Entry	RCOOH	RC(O)$NHNH_2$	Product	Yield[a] (%)
1				85 (85)[b]
2				85 (50)[b]
3				94 (80)[b]
4				86 (30)[b]
5				95 (75)[b]
6				83
7				86
8				92
9				80
10				99
11				85

[a] Isolated yield after purification.
[b] Isolated yield using DMC as the reagent (Scheme 2).

CH_3CN under microwave heating conditions without the need of isolating the diacyl hydrazide intermediate. Thus, in the presence of 2 equiv CCl_3CN and 3 equiv of PS-PPh_3, a variety of 1,3,4-oxadiazoles could be efficiently synthesized from the requisite carboxylic acid and acid hydrazide in acetonitrile at 150 °C for 20 min in one simple operation (Table 1).[9] Of note was the observation that 2 equiv CCl_3CN was necessary to achieve the optimal conversion to the desired 1,3,4-oxadiazoles. With 1.5 equiv of CCl_3CN, both the diacyl hydrazide intermediates and the product 1,3,4-oxadiazoles were observed by LC/MS analysis of the crude reaction. In addition, significantly, no base was necessary for reaction success. Good to excellent yields were obtained as annotated in Table 1. This one step procedure was found to be quite general and worked well for a variety of alkyl and aryl carboxylic acids as well as alkyl and aryl acid hydrazides. This feature is very desirable for library production as diverse substituent patterns are often used with one set of reaction conditions in a single library. In many cases, the cyclized product 1,3,4-oxadiazoles were the only peak seen in crude LC/MS[10] and the isolated yields were more than 85%. In addition, the reaction is very easy to workup by simple filtration



Scheme 3. Synthesis of diacyl hydrazide **3**.



Scheme 4. Conversion of **3** to 1,3,4-oxadiazole **4** with PS-PPh_3/CCl_3CN.

of the resin and evaporation of the solvents. In most cases, a quick, simple flash silica column afforded the desired product 1,3,4-oxadiazole in high purity.

In summary, we have developed a rapid and efficient method for the synthesis of 1,3,4-oxadiazoles in high yields using readily available carboxylic acids and acid hydrazides in one simple step under mild reaction conditions. The use of solid-phase reagents in combination with microwave heating greatly simplified the purification process, and allowed us to quickly identify the optimal reaction condition and obtain high yields and operational efficiency. This method is not only suitable for the preparation of either individual analogues, but also the production of libraries using automation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.131.

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9. General procedure: A Smith Process vial (0.5–2 ml) was charged with a stir bar. To the vessel were added 0.1 mmol of the carboxylic acid and 0.11 mmol of the acid hydrazide in 1.5 ml dry CH_3CN. 0.3 mmol PS-PPh_3 (3 mmol/g) was added to the reaction mixture, followed by 0.2 mmol CCl_3CN. The reaction vessel was sealed and heated in microwave to 150 °C for 20 min. After cooling, the reaction vessel was uncapped and the resin was filtered and washed with additional CH_3CN. The desired 1,3,4-oxadiazoles were isolated by flash chromatography. All products thus obtained were greater than 98% pure as determined by LC/MS and ^1H NMR analysis.
10. In most cases, LC/MS analysis of the crude materials showed the purities of the products are greater than 90%.