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A mild, one-pot preparation of 1,3,4-oxadiazoles

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ABSTRACT

A mild and efficient one-pot protocol for the synthesis of 1,3,4-oxadiazoles from carboxylic acids and acylhydrazides was developed. Diacylhydrazide formation via HATU coupling followed by addition of Burgess reagent afforded the corresponding 1,3,4-oxadiazoles in 63–96% yields at room temperature. The reaction conditions are tolerant of a variety of functional groups, including esters, nitriles, alkynes, olefins, alkyl halides, phenols, carbamates and sulfonamides.

1. Introduction

1,3,4-Oxadiazoles are typically considered as bioisosteres for carboxylic acids, esters and amides.[1–3] Over the years, numerous methods have been employed in the preparation of this class of heterocycles.[4–6] Brain and co-workers developed a procedure wherein they first prepared and isolated diacylhydrazides. In a second step, cyclodehydration with Burgess reagent by heating under microwave irradiation gave the resulting 1,3,4-oxadiazole.[4] Since then, several new protocols utilizing microwave heating have been reported in the preparation of 1,3,4-oxadiazoles.[5] While microwave irradiation is an excellent tool for reducing reaction time, sensitive functionalities are often incompatible with elevated temperatures. To address this limitation, we have developed a mild and convenient one-pot protocol for the synthesis of 1,3,4-oxadiazoles from carboxylic acids and hydrazides. Diacylhydrazide formation via HATU coupling was followed by addition of Burgess reagent to the same reaction pot to induce cyclodehydration at room temperature, typically within 1–3 hours.[7]

2. Results and discussion

Throughout our study, the hydrazide (phenyl hydrazide) was kept constant while the carboxylic acids were varied (Scheme 1). Our first goal was to evaluate how this transformation would respond to electronic and steric alterations (Table 1). Both electron-donating (entry 2) and electron-withdrawing (entry 3) substrates afforded high yields of the desired 1,3,4-oxadiazoles. On the other hand, introduction of steric bulk required manipulation of the standard reaction conditions; this was demonstrated by the easy conversion of 2-methylbenzoic acid (entry 5) to the desired oxadiazole in less than two hours in 80% yield. To the contrary, reaction with the more sterically encumbered 2,6-dimethylbenzoic acid (entry 6) required heating at reflux for 2 days to form the diacylhydrazide. Subsequent addition of Burgess reagent generated the desired product in 63% yield after stirring overnight at room temperature. Alkyl substrates **7** and **8** demonstrated that the scope of this reaction can be expanded beyond aryl substrates.

Our mild reaction conditions offer considerable functional group tolerance (Table 2). The reaction worked well in the presence of a wide variety of functionalities, including nitriles, esters and alkynes (entries 1, 2, and 3, respectively). We found that olefins are also highly compatible (entry 4) and even substrates containing alkyl halides (entry 5) resulted in excellent yields of oxadiazole formation. Heteroaryl substrates (entries 6 and 7) also produced oxadiazoles in excellent yields.

The limitations of our one-pot protocol greatly depended upon the substrates' compatibility with the Burgess reagent. During the optimization of our reaction conditions, we discovered that, after successful diacylhydrazide formation via HATU coupling, the first equivalent of Burgess reagent was consumed without any evidence of the diacylhydrazide undergoing cyclodehydration. We speculated that this first equivalent is consumed by the 7-azabenzotriazole generated in the HATU coupling. Formation of the 1,3,4-oxadiazole only occurred upon addition of another 1.5 equivalent of Burgess reagent. Thus, a total of 2.5 equivalents of Burgess reagent was required to drive the reactions to completion.

In the course of our substrate exploration, this hypothesis was further validated by the results obtained in experiments where the carboxylic acid moiety contained heteroatoms acting as potential nucleophiles (Table 3). After successful diacylhydrazide formation of entry 1, addition of Burgess reagent lead to a variety of side reactions (observed by LC–MS). One major side product observed included a species with a mass consistent with the intermediate shown in Figure 1. Entry 4 gave a similar result, while entry 5 afforded a complex mixture of unidentifiable side products.

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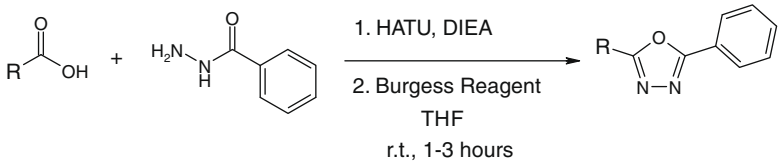
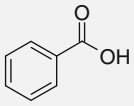
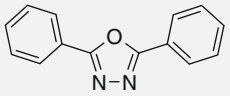
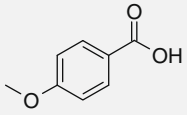
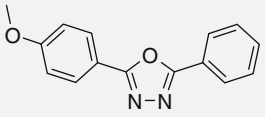
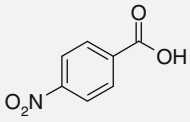
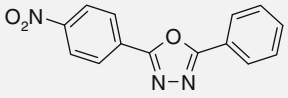
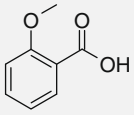
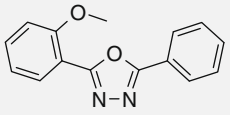
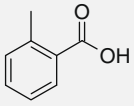
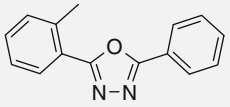
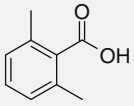
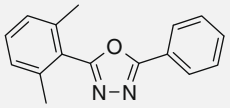
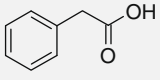
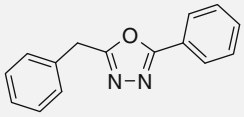
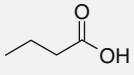
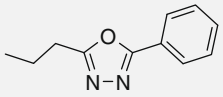


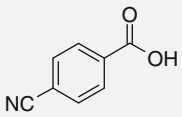
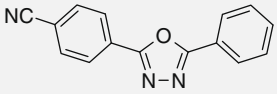
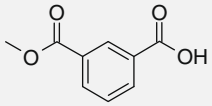
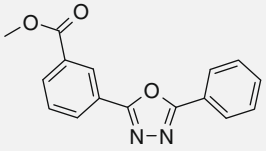
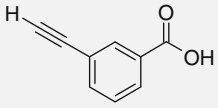
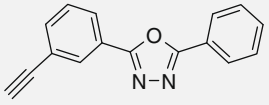
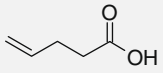
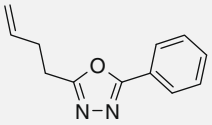
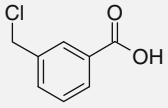
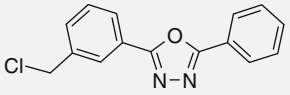
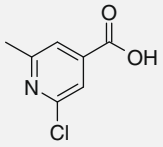
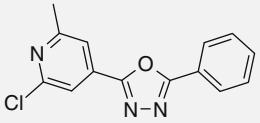
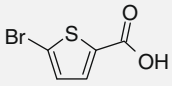
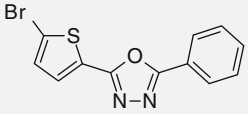
Scheme 1.

Table 1
Electronic and steric effects

Entry	Acid	Product	Yields[a,b,c] (%)
1			88
2			88
3			96
4			86
5			80
6			63[d,e]
7			94
8			89

[a] Yields refer to pure (by ^{1}H NMR and LC–MS) product after column chromatography.
[b] All reactions were performed using 1.0 equiv phenyl hydrazide, 1.0 equiv carboxylic acid, 1.0 equiv HATU, 2.0 equiv Hunig's base, and 2.5 equiv Burgess reagent in reaction concentration of 0.11 M THF, unless otherwise noted.
[c] All reactions were complete in less than 3 h unless otherwise noted.
[d] Required reflux heating for two days to afford diacylhydrazide, and overnight stirring at room temperature to form oxadiazole.
[e] Required 6.0 equiv Burgess reagent for cyclodehydration to go to completion.

Table 2
Functional group compatibility

Entry	Carboxylic acid	Product	Yield[a,b,c] (%)
1			96
2			86
3			95
4			88
5			95
6			96
7			95

[a] Yields refer to pure (by ^{1}H NMR and LC–MS) product after column chromatography.
[b] All reactions were performed using 1.0 equiv phenyl hydrazide, 1.0 equiv carboxylic acid, 1.0 equiv HATU, 2.0 equiv Hunig's base, and 2.5 equiv Burgess reagent and reaction concentration of 0.11 M THF, unless otherwise noted.
[c] All reactions were complete in less than 3 h unless otherwise noted.

Table 3
Functional group compatibility

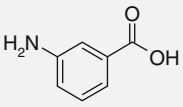
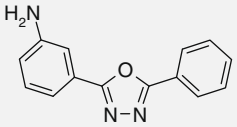
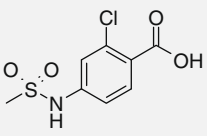
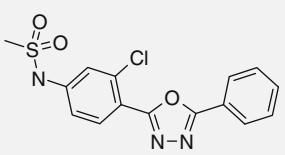
Entry	Carboxylic acid	Product	Yield[a,b,c] (%)
1			0
2			69

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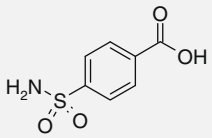
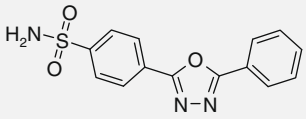
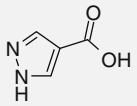
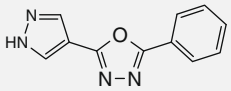
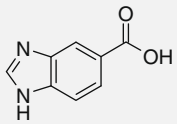
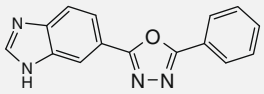
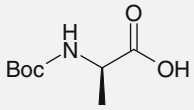
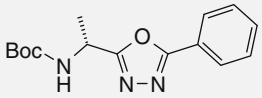
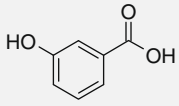
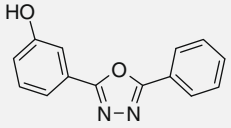
Table 3 (*continued*)

Entry	Carboxylic acid	Product	Yield[a,b,c] (%)
3			71
4			0
5			0
6			69
7			77

[a] Yields refer to pure (by ^{1}H NMR and LC–MS) product after column chromatography.
[b] All reactions were performed using 1.0 equiv phenyl hydrazide, 1.0 equiv carboxylic acid, 1.0 equiv HATU, 2.0 equiv Hunig's base, and 2.5 equiv Burgess reagent and reaction concentration of 0.11 M THF, unless otherwise noted.
[c] All reactions were complete in less than 3 h unless otherwise noted.

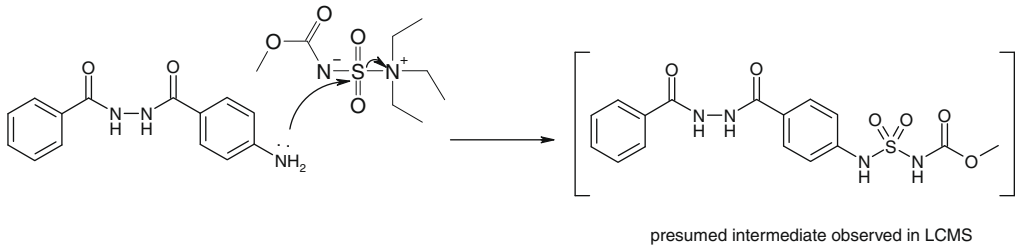


Figure 1. Side reaction of aniline functionality with Burgess reagent.

Interestingly, incorporation of electron-withdrawing substituents (entries 2 and 3) attenuated the nucleophilicity of the nitrogen, such that less of the undesired side reactions were observed. Consequently, entries 2 and 3 gave respectable yields of the desired 1,3,4-oxadiazole products (69% and 71% yields, respectively). For the same reason, useful chemical synthon Boc-D-alanine (entry 6) gave good yields of the desired 1,3,5-oxadiazole. Finally, phenolic substrates (entry 7) did not have the same problem as aniline counterpart (entry 1) and gave oxadiazole in good yield.

3. Conclusions

In conclusion, we have developed a mild and efficient one-pot protocol for the synthesis of 1,3,4-oxadiazoles from carboxylic acids and acyl hydrazides at room temperature. Oxadiazole formation proceeds equally well for electron-withdrawing as well as electron-donating substrates, while steric hindrance prolonged reaction times. The mild reaction conditions are tolerant of various functional groups, including esters, alkynes, nitriles, alkyl halides, olefins, phenols, carbamates and sulfonamides.

References and notes

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7. *Typical experimental procedure*: (Table 2, entry 4) *2-(3-buten-1-yl)-5-phenyl-1,3,4-oxadiazole*: A solution of benzohydrazide (150 mg, 1.102 mmol),4-pentenoic acid (110 mg, 1.102 mmol), HATU (419 mg, 1.102 mmol), and Hunig's base (0.385 mL, 2.203 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature for 45 min. Next, Burgess reagent (656 mg, 2.75 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was adsorbed onto silica gel and the crude material was purified via silica gel chromatography (5–40% ethyl acetate/hexanes as eluent) to give 2-(3-buten-1-yl)-5-phenyl-1,3,4-oxadiazole (194 mg, 88% yield) ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.96 (dd, J = 7.78, 1.74 Hz, 2 H), 7.54–7.62 (m, 3H), 5.88 (m, 1H), 5.10 (dd, J = 17.03, 1.65 Hz, 1H), 5.01 (dd, J = 10.26, 1.47 Hz, 1H), 3.03 (t, J = 7.42 Hz, 2H), 2.51–2.55 (m, 2H). LC–MS (ES$^+$) m/z, 200.63 [M+H].