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A mild and efficient one pot synthesis of 1,3,4-oxadiazoles from carboxylic acids and acyl hydrazides

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Abstract—A convenient one pot method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acids and acyl hydrazides is reported. Acid activation with CDI, followed by coupling with the desired acylhydrazide and dehydration in the same pot with Ph_3P and CBr_4 affords the corresponding 1,3,4-oxadiazoles in good yield. The scope of the acid and acylhydrazide components is presented.

Oxadiazoles are nonnaturally occurring five-membered aromatic heterocycles with utility in synthetic and medicinal chemistry. Cycloaddition of 1,3,4-oxadiazoles with alkynes are known to provide furans following the extrusion of nitrogen gas.[1] In the field of medicinal chemistry, oxadiazoles are utilized as ester or amide surrogates. Biologically relevant entities containing the 1,3,4-oxadiazole motif include the HIV integrase inhibitor **1** and the angiogenesis inhibitor **2** (Fig. 1).[2,3]

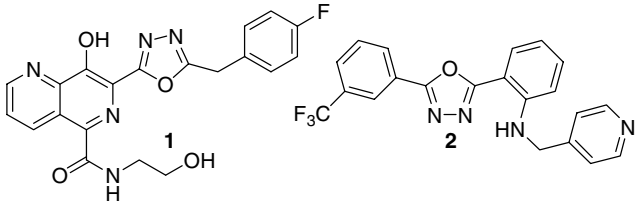

Figure 1. Biologically active compounds with the 1,3,5-oxadiazole motif.

To the best of our knowledge, limited methodology exists for the synthesis of 1,3,4-oxadiazoles. Typically, a two step protocol is utilized where the acylhydrazide and carboxylic acid partners are coupled under amide bond forming conditions and the resulting product is isolated and dehydrated using standard reagents.[4–6] A few one pot methods have been reported in the literature, but these often require activated acids or forcing conditions and are limited in substrate scope.[7–9] We wished to develop a more general and convenient one pot method for the synthesis of these useful heterocycles.

Our previous experience accrued from the dehydration of diacylated hydrazides toward the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles showed that CBr_4 and Ph_3P were the optimal reagents for this transformation. High yields and good substrate compatibility were consistently observed under these conditions. Hence we focused on performing the coupling of the acid and acyl hydrazide partners under conditions compatible with our preferred cyclodehydrating reagents.

Gratifyingly, activation of *N*-Boc-(L)-Phe-OH with carbonyl diimidazole (CDI), followed by the addition of benzoyl hydrazide provided the pivotal bis-acylhydrazide adduct by LC/MS. With the addition of CBr_4 and Ph_3P, the dehydration proceeded smoothly to provide the desired oxadiazole **3** in high yield (Table 1).[10,11] Strictly anhydrous conditions were not required for this transformation, and the product mixture was purified directly by normal phase chromatography without the need for an aqueous workup.[12] The entire sequence could be performed at 0 °C or room temperature, and the formation of the bis-acylhydrazide intermediate could be readily monitored by LC/MS or TLC. Polymer supported Ph_3P could be utilized for the dehydration step with only a small loss in yield. This reaction sequence displayed a surprising solvent dependence, as

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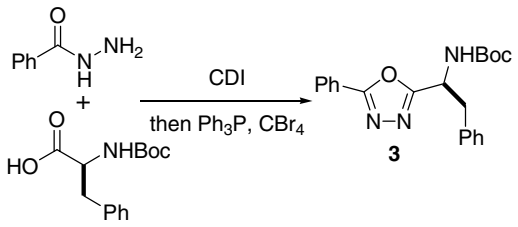
Table 1. Solvent and temperature scope



Solvent	Temperature (°C)	Yield[a] (%)
CH_2Cl_2	0	83
CH_2Cl_2	RT	87
CH_2Cl_2[b]	0→RT	75
THF	0→RT	50
DMF	RT	0

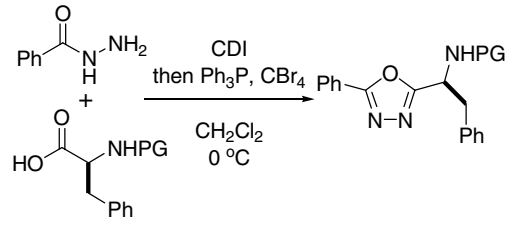
[a] Isolated yield.
[b] Polymer supported Ph_3P was used in this example.

the coupling and dehydration proceeded very sluggishly in THF. Incomplete coupling was observed with DMF, and none of the desired product **3** was detected by LC/MS after the addition of Ph_3P and CBr_4.

We then surveyed this one pot methodology with respect to the scope of nitrogen protecting groups (Table 2). Cbz and acetamide also proved to be compatible with this sequence, providing heterocycles **4** and **5**, respectively, with high yields. The base sensitive Fmoc and TFA functionalities also proved to be compatible with these conditions and provided oxadiazoles **6** and **7** in good yield.

The reactions of a diverse set of acids with benzoyl hydrazide are shown in Table 3. The basic amine moiety of *N*-benzyl-Pro-OH was tolerated to provide **8** with reasonable efficiency. Epimerization prone *N*-Boc protected phenylglycine provided **9** with minimal racemization.[13] Our methodology was compatible with sterically hindered acids, as demonstrated by the synthesis of oxadiazole **10** in good yield. Conjugation of the acid with π-functionality proved to be detrimental, providing the corresponding oxadiazole **11** in only 23% yield. We suspect that this is primarily due to the sluggishness of

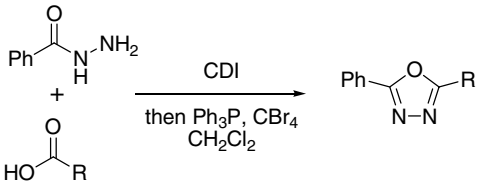
Table 2. N-Protecting group compatibility

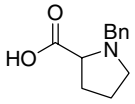
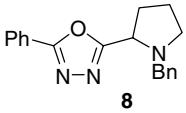
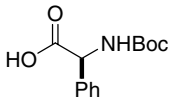
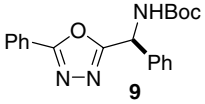
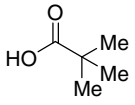
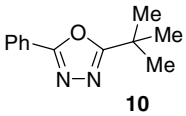
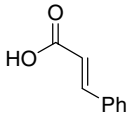
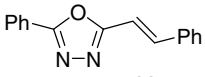
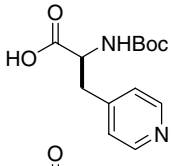
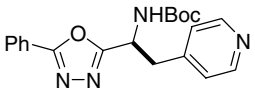
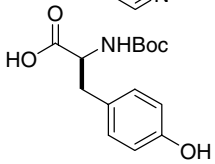
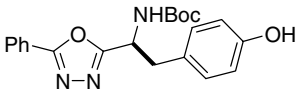


PG	Product	Yield[a] (%)
Boc	**3**	83
Cbz	**4**	81
Ac	**5**	75
Fmoc	**6**	73
TFA	**7**	57

[a] Isolated yield.

Table 3. Scope of acid coupling partner



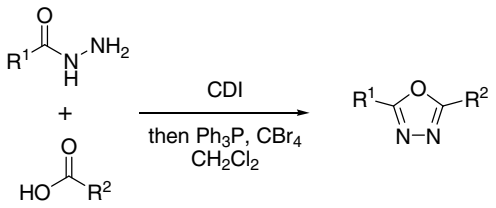
Acid	Product	Yield[a] (%)
	 **8**	52
	 **9**	66
	 **10**	73
	 **11**	23[b]
	 **12**	0[c]
	 **13**	0[c]

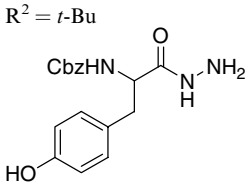
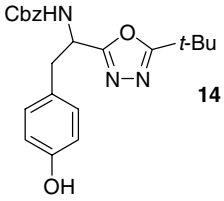
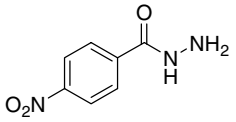
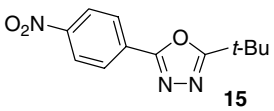
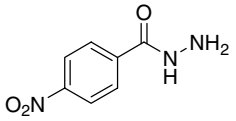
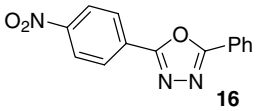
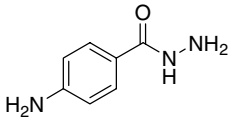
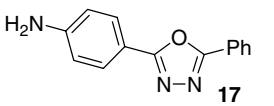
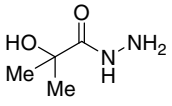
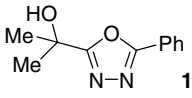
[a] Isolated yield.
[b] The coupling of the activated acid with benzoyl hydrazide was heated to 40 °C.
[c] The diacylhydrazide coupling intermediate was not detected by LC/MS.

the coupling step, as heating was required to obtain any diacylated hydrazide adduct. The dehydration process appeared to be unaffected by this type of substitution, as the diacylated hydrazide was converted to the desired oxadiazole at room temperature. Incorporation of nucleophilic functionality on the acid partner was not feasible as both *N*-Boc-4-pyridylalanine and *N*-Boc-4-tyrosine did not provide oxadiazoles **12** and **13**, as determined by LC/MS analysis. We speculate that this is due to the undesired reaction of the activated acid with the nucleophilic functionality embedded within the coupling partner.

The acylhydrazide component proved to be tolerant of a variety of functional groups in this one pot sequence (Table 4). Phenolic, aniline, and tertiary hydroxyl bearing acyl hydrazides coupled effectively with activated acids and cyclodehydrated to provide oxadiazoles **14**, **17**, and **18** in reasonable yields. The presence of the elec-

Table 4. Acyl hydrazide compatibility

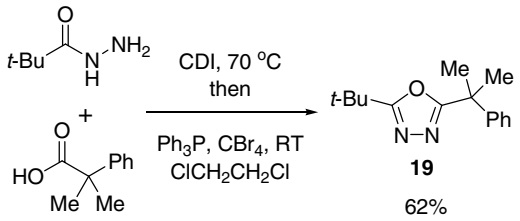


Hydrazide	Product	Yield[a] (%)
$R^2 = t$-Bu		
	 **14**	90
	 **15**	75
$R^2 = Ph$		
	 **16**	54[b]
	 **17**	37[b]
	 **18**	62[c]

[a] Isolated yield.
[b] The coupling of the activated acid with the respective acylhydrazide was heated to 40 °C.
[c] The coupling reaction proceeded at room temperature over 15 h.

tron withdrawing nitro group on the benzoyl hydrazide moiety proved to be compatible with our conditions as the reaction proceeds at room temperature with pivalic acid to give **15** in good yield. When the identical hydrazide is coupled with benzoic acid, heating is required for good conversion and oxadiazole **16** is produced in lower yield, again illustrating the problematic nature of conjugated acids in this reaction sequence.

As a further demonstration of the utility of this methodology, the coupling/dehydration of two sterically demanding partners to provide the corresponding 1,3,4-oxadiazole is depicted in Scheme 1. The activation of α,α-dimethylphenylacetic acid and coupling with pivaloyl hydrazide proceeded at 70 °C to cleanly afford the coupled adduct as observed by LC/MS. Addition of CBr_4 and Ph_3P and subsequent dehydration at room temperature provided oxadiazole **19** in 62% yield.



Scheme 1. Coupling of sterically demanding partners.

In summary, we have developed a mild and convenient one pot method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles that is compatible with functionality on both the acid and acyl hydrazide coupling partners. Strictly anhydrous conditions are not required, and the product mixture can be loaded directly onto a silica gel column for purification, obviating the need for an aqueous workup. The only functional group incompatibility that we observed was the presence of nucleophilic functionality on the acid partner. Overall, the efficiency of this process is mostly limited by the coupling step, as once the diacylhydrazide is generated, dehydration proceeded without exception. The use of unsaturated carboxylic acids may require longer reaction times or heating to induce reasonable conversion. We expect this methodology to be useful in the context of both single compound and library synthesis.

Acknowledgements

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References and notes

1. Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361, and references cited therein.
2. Johns, B. A. PCT Int Appl. WO 2004101512.
3. Piatnitski, E.; Kiselyov, A.; Doody, J.; Hadari, Y.; Ouyang, S.; Chen, X. PCT Int Appl. WO 2004052280.
4. Brown, P.; Best, D. J.; Broom, N. J. P.; Cassels, R.; O'Hanlon, P. J.; Mitchell, T. J.; Osborne, N. F.; Wilson, J. M. *J. Med. Chem.* **1997**, *40*, 2563 ($Ph_3P/CCl_4/Et_3N$).
5. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275 (polymer supported Burgess reagent).
6. Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331 ($SOCl_2$).
7. Mashrqui, S. H.; Ghandigaonkar, S. G.; Kenny, R. S. *Synth. Commun.* **2003**, *33*, 2541.
8. Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989.
9. Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 105.
10. *Representative procedure*: To a solution of *N*-Boc-(L)-Phe-OH (58 mg, 0.22 mmol) in 2 mL CH_2Cl_2 at 0 °C was added CDI (36 mg, 0.23 mmol). After 30 min, benzoyl hydrazide (30 mg, 0.22 mmol) was added. The coupling was allowed to proceed at 0 °C for 45 min then CBr_4 (146 mg, 0.441 mmol) and Ph_3P (116 mg, 0.441 mmol) were added in one portion. The dehydration step was allowed to proceed at 0 °C for 2 h and the reaction was poured onto a silica gel column for purification via normal phase chromatography (40 g silica, 30 mL/min, 5→50%

EtOAc/hex) to afford the desired product **3** (66 mg, 0.18 mmol, yield 83%) as a white solid.
11. In comparison, coupling *N*-Boc-(L)-Phe-OH and benzoyl hydrazide with EDC, isolating the bis-acyl hydrazide and dehydrating under identical conditions provided **3** in 92% yield.
12. The reactions could be run in undried glassware under ambient atmosphere.
13. This reaction proceeded with ~4% racemization as confirmed by chiral HPLC analysis (ChiralPak AD column, 60% EtOH/hex with 1 mL/L added diethylamine) of the individual enantiomers of **9**. For a review detailing the challenges in the synthesis of and late stage manipulations involving aryl glycines, see: Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Wissinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.