

General synthesis of tetrasubstituted alkenyl-1,3,4-oxadiazoles

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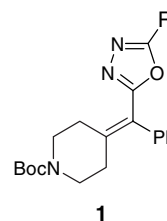
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Abstract—Tetrasubstituted alkenyl-1,3,4-oxadiazoles were synthesized in moderate to excellent yield, under mild conditions and in the presence of sensitive functional groups, via the cyclization of diacylhydrazides using PPh_3 and hexachloroethane in the presence of H nig's base. An efficient one-pot acylation/cyclization approach for the conversion of acylhydrazides to 1,3,4-oxadiazoles is also described. The complexity of our substrate as well as the wide range of functional groups incorporated substantially broadens the scope of this methodology.

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The replacement of acid and ester functionality in medicinal chemistry continues to be a popular strategy in the search for compounds with superior pharmacokinetic profiles. In particular, the 1,3,4-oxadiazole ring is increasingly used and has found application in several areas.¹ Consequently, the synthesis of this heterocycle has attracted considerable attention and a wide variety of methods have been used for its assembly.² By far the most common strategy involves the dehydrative cyclization of diacylhydrazides, usually with strongly acidic reagents such as POCl_3 ,³ SOCl_2 ,⁴ P_2O_5 ,⁵ H_2SO_4 ,⁶ or PPA .⁷ More recently, however, several methods have been developed using essentially neutral conditions and cyclization mediators such as Tf_2O ⁸ and HMDS/TBAF ,⁹ as well as solid supported cyclization reagents.¹⁰

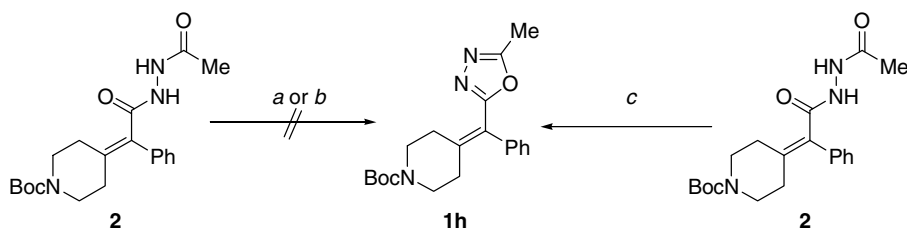
Recently, we required a convenient synthesis of vinyl-1,3,4-oxadiazoles of type **1**. A search of the literature revealed that 1,3,4-oxadiazoles as substituents on tetrasubstituted olefins are rare.¹¹ In addition to the complex nature of our substrate, we also required very mild conditions, which would allow the incorporation of sensitive functional groups, while leaving our protecting group intact. Unfortunately, we found that several of the standard conditions for diacylhydrazide cyclization, gave only complex mixtures of products (Scheme 1).



We reasoned that given the success of the PPh_3/X_2 combination in such processes as halogenation of alcohols,¹² these conditions, when properly buffered, might result in efficient amide dehydration and subsequent cyclization. In fact, a further survey of the literature showed that for a limited number of cases similar conditions had been used to effect this transformation. Mazurkiewicz and Grymel¹³ showed that *N*-benzoyl-*N'*-acetylhydrazine and *N,N'*-dibenzoylhydrazine were converted to the corresponding oxadiazoles in good to excellent yields with $\text{PPh}_3\cdot\text{Br}_2$, $\text{PPh}_3\cdot\text{CBr}_4$, and $\text{PPh}_3\cdot\text{CCl}_4$ in refluxing CH_2Cl_2 in the presence of NEt_3 . A limited number of *N*-acylsemicarbazides are also converted smoothly to the corresponding 2-aminooxadiazoles under these conditions. We were similarly encouraged by a report by Polanc¹⁴ who effected similar chemistry making use of $\text{PPh}_3/(\text{BrCl}_2\text{C})_2$. While the conditions reported would be ideal for our purposes, the scope of the reaction was not investigated. Only a limited number of examples were reported starting only from 1,4-disubstituted semicarbazides to give 2-amino-1,3,4-oxadiazoles.

In our study, we were delighted to observe that when a solution of diacylhydrazide **2** was treated with

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Scheme 1. Reagents and conditions: (a) $\text{POCl}_3/\text{CH}_3\text{CN}/\text{NEt}_3$; (b) $\text{Tf}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{NEt}_3$; (c) $\text{PPh}_3/\text{Cl}_3\text{CCl}_3/i\text{-Pr}_2\text{NEt}/\text{CH}_3\text{CN}$ (75%).

hexachloroethane in acetonitrile in the presence of Hünig's base and PPh_3 , a very fast cyclization occurred at room temperature. Subsequent routine aqueous workup afforded the desired oxadiazole in good yield (Scheme 1). Under these conditions, a series of diacylhydrazides¹⁵ **2a–j** were smoothly cyclized to give oxadiazoles **1a–j** in moderate to excellent yields (Table 1).¹⁶

These conditions are very mild and the olefin functionality does not seem to interfere with the course of the reaction. A wide variety of functional groups are tolerated, for example, bromomethyl (entry 2) and silyloxymethyl (entry 4). Additionally, heteroatom functionality (e.g., OMe, entry 3) and the versatile ester group (entry 5) may also be incorporated into the 2-position of the oxadiazole ring. Moreover, the base-sensitive Fmoc-protected azetidione (entry 9) was well tolerated under these conditions, as was the trityl protected aziridine (entry 10).

Having established the conditions of the cyclization step, we hoped that the synthesis could be made more efficient by carrying out a one-pot procedure¹⁷ directly from the monoacylhydrazide **3**, thus eliminating one purification step. Disappointingly, treatment of **3** with acetyl chloride in the presence of Hünig's base gave only a complex mixture, suggesting that acid chlorides may

be unsuitable for this conversion in acetonitrile. However, when **3** was treated with acetic anhydride in acetonitrile containing Hünig's base, clean conversion to the diacylhydrazide was effected (based on LCMS and TLC analyses). Subsequent addition of PPh_3 , followed by hexachloroethane, resulted in complete cyclization to the oxadiazole after about 15 min at room temperature. Standard workup and purification afforded the 1,3,4-oxadiazole **1h**, which was identical with the previously prepared material. A number of acylating agents was used in an analogous manner to afford oxadiazoles **1k–p** (Table 2).

As can be seen in Table 2, the yields of the one-pot procedure are generally good and again a variety of functional groups are tolerated.¹⁸ For example, the use of trifluoroacetic anhydride furnishes a 2-trifluoromethyl-oxadiazole (entry 3), while a nitrogen functional group can be installed using *N,N*-dimethylcarbonyl chloride (entry 4). Interestingly, the latter was found to react smoothly with **3**, in contrast to simple acid chlorides, which gave complex mixtures.

In conclusion, we have demonstrated that $\text{PPh}_3/\text{Cl}_3\text{CCl}_3/i\text{-Pr}_2\text{NEt}$ are efficient conditions for the cyclization of diacylhydrazides to give a series tetrasubstituted alkenyl-1,3,4-oxadiazoles, where standard methods failed. We have also significantly expanded the scope of this reaction, demonstrating that a wide variety of functionality is tolerated, including the tetrasubstituted olefin of the core structure. An efficient one-pot

Table 1. Synthesis of 1,3,4-oxadiazoles from diacylhydrazides

Entry	SM	R	Product	Yield (%)
1	2a	<i>c</i> -Pr	1a	95
2	2b	CH_2Br	1b	53
3	2c	OMe	1c	85
4	2d	CH_2OTBS	1d	74
5	2e	CO_2Et	1e	54
6	2f	H	1f	70
7	2g	<i>c</i> -Bu	1g	98
8	2h	Me	1h	75
9	2i		1i	75
10	2j		1j	68

Table 2. One-pot synthesis of 1,3,4-oxadiazoles

Entry	Acylating agent	R	Product	Yield (%)
1	Ac_2O	Me	1h	88
2	$(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$	Et	1k	68
3	TFAA	CF_3	1l	77
4	ClCONMe_2	NMe_2	1m	81
5	$(t\text{-BuCO})_2\text{O}$	<i>t</i> -Bu	1n	95
6	$(\text{PhCO})_2\text{O}$	Ph	1o	78
7	Methacrylic anhydride		1p	56

procedure for the conversion of acylhydrazides to 1,3,4-oxadiazoles has also been demonstrated. The latter approach is potentially amenable to parallel synthesis strategies for the production of a wide variety of functionalized 1,3,4-oxadiazoles, given the large number of monoacylhydrazides, which are commercially available and the mild conditions used for effecting the key cyclization step.

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- The diacylhydrazides were prepared either by coupling of the acid corresponding to **3**, with an excess of the appropriate hydrazide (AcNHNH₂, HCONHNH₂, or MeOCONHNH₂) in the presence of EDCI/HOBt in DMF, or by acylation of **3** with the corresponding acid chloride in H₂O/dioxane (1:1) and Na₂CO₃ as base. The latter procedure is exemplified by the preparation of **2b**: To a solution of **3** (0.220 g, 0.66 mmol) in dioxane/water (1:1, 4 mL) was added Na₂CO₃ (0.07 g, 0.66 mmol) and the solution was cooled to 0 °C. Bromoacetyl bromide (0.055 mL, 0.63 mmol) was added slowly. The mixture was allowed to stir at 0 °C for 1 h and was then quenched with satd NH₄Cl and extracted with EtOAc (×3). The combined organic layers were washed (H₂O, brine), dried (Na₂SO₄), and concentrated in vacuo to afford diacyl hydrazide **2b** (0.209 mg, 70%), which was of sufficient purity for use in the following step. ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.40 (m, 3H), 7.21–7.24 (m, 2H), 4.09 (s, 2H), 3.16 (t, J = 5.7 Hz, 2H), 3.38 (t, J = 5.7 Hz, 2H), 2.87 (t, J = 5.7 Hz, 2H), 2.17 (t, J = 5.7 Hz, 2H), 1.45 (s, 9H). LCMS *m/e* 452 (M+H)⁺. Monoacylhydrazide **3** was prepared by EDCI/HOBt coupling of the corresponding acid with an excess of hydrazine monohydrate.
- Representative procedure for the cyclization of diacylhydrazides: To a suspension of diacylhydrazide **2f** (0.106 g, 0.294 mmol) in CH₃CN (2 mL) was added *i*-Pr₂NEt (0.30 mL, 1.7 mmol) and PPh₃ (0.137 g, 0.523 mmol), followed after 5 min by hexachloroethane (0.092 mg, 0.389 mmol). After stirring the mixture at room temperature for 4 h the solvent was removed in vacuo and the residue partitioned with H₂O/EtOAc. The organic phase was separated and the aqueous phase was re-extracted with EtOAc. The combined organic phases were washed (H₂O, brine), dried (Na₂SO₄) and evaporated, and the residue was purified by preparative HPLC to give **1f** (0.0504 g, 50%) as a colorless solid: ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.41–7.36 (m, 3H), 7.18–7.16 (m, 2H), 3.59 (dd, J = 5.6, 5.8 Hz, 2H), 3.43 (dd, J = 5.5, 5.9 Hz, 2H), 2.91 (dd, J = 6.1, 5.5 Hz, 2H), 2.31 (dd, J = 5.8, 5.5 Hz, 2H), 1.45 (s, 9H). LCMS: *m/e* 342 (M+H)⁺.
- Polanc has demonstrated a similar one-pot protocol for a limited number of substrates starting from monoacylhydrazides and isocyanates to give 2-amino-1,3,4-oxadiazoles (see Ref. 14).
- Representative procedure for the one-pot acylation/cyclization: To a solution of hydrazide **3** (1.00 g, 3.02 mmol) and *i*-Pr₂NEt (3.62 mL, 20.8 mmol) in CH₃CN (20 mL)

was added acetic anhydride (0.357 mL, 3.78 mmol) and the mixture was allowed to stir for 1 h at room temperature. To this mixture was added PPh₃ (3.25 g, 12.39 mmol), followed by hexachloroethane (1.65 g, 6.95 mmol). The mixture was allowed to stir for 30 min

and then it was worked up and purified as above (cf. Ref. 16) to afford **1h** (0.946 mg, 88%) as a colorless solid: ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.34 (m, 3H), 7.39–7.23 (m, 2H), 3.56 (m, 3H), 3.40 (m, 3H), 2.85 (br m, 2H), 2.33 (s, 3H), 2.20 (m, 2H). LCMS: *m/e* 356 (M+H)⁺.