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Mild and convenient one-pot synthesis of 1,3,4-oxadiazoles

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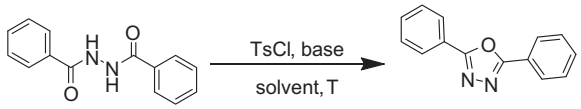
ABSTRACT

A mild, general, convenient, and efficient one-pot synthesis of 2-phenyl-5-substituted-1,3,4-oxadiazoles is described. Both (hetero)aryl and alkyl carboxylic acids were efficiently condensed with benzohydrazide in the presence of TBTU to give diacylhydrazine intermediates. The latter underwent a smooth TsCl-mediated cyclodehydration reaction to afford 2-phenyl-5-substituted-1,3,4-oxadiazoles in good to very good yields.

The 1,3,4-oxadiazole motif has been extensively used for many years by medicinal chemists as a bioisosteric replacement of acid, ester, and amide functionalities in compounds exhibiting a wide range of biological activities.[1] Among the reported methodologies for the synthesis of 1,3,4-oxadiazoles, the cyclodehydration reaction of 1,2-diacylhydrazines is often found in the literature.[2] In particular, dehydrating agents such as $SOCl_2$ and highly toxic $POCl_3$ are widely employed.[3] However, harsh reaction conditions, such as high temperatures and large excess of the dehydrating reagent, are usually required. Milder cyclodehydration reactions have been mediated by 2-chloro-1,3-dimethylimidazolinium chloride,[4] PPh_3/I_2, and PPh_3/CX_4 systems (X = Cl or Br)[5] or the expensive Burgess reagent.[6] The readily available and relatively cheap 4-methylbenzenesulfonyl chloride has also been described to promote 1,3,4-oxadiazole formation from 1,2-diacylhydrazines.[7] In addition, microwave-mediated syntheses of 1,3,4-oxadiazoles have also been reported.[8]

Very recently, a few efficient one-pot protocols appeared in the literature. Dickson and Li prepared 2,5-disubstituted 1,3,4-oxadiazoles starting from benzohydrazide and a variety of carboxylic acids.[9] Nevertheless, quite expensive HATU, as an amide coupling agent, and Burgess reagent, as dehydrating system, were utilized. On the other hand, Augustine et al. described the use of T3P® acting both as the coupling and the cyclodehydration agent in the synthesis of 1,3,4-oxadiazoles from carboxylic acids and hydrazides.[10] Despite the wide generality and the high efficiency of the above-mentioned methodologies, some limitations still remain. As a matter of fact, the high cost of the reagents and the need to store the Burgess reagent at low temperatures do not make these procedures appealing for large-scale preparations.

Table 1
TsCl-mediated cyclodehydration of **3a**



3a **4a**

Entry	Solvent	Base	*T* (°C)	Yield[a,b] (%)	Yield[c,d] (%)
1	MeCN	TEA	25	>99	95
2	MeCN	Pyridine	40	0	—
3	MeCN	DBU	25	85	—
4	MeCN	K_2CO_3	25	>99	95
5	CH_2Cl_2	TEA	25	>99	95
6	CH_2Cl_2	Pyridine	40	0	—
7	CH_2Cl_2	DBU	25	69	—
8	CH_2Cl_2	K_2CO_3	25	>99	—
9	Acetone	TEA	40	>99	96
10	Acetone	Pyridine	40	0	—
11	Acetone	DBU	25	86	—
12	Acetone	K_2CO_3	40	>99	90

[a] A mixture of **3a** (1 mmol), the base (3 equiv) and TsCl (1.5 equiv) in the solvent (4.8 ml) was stirred at the indicated temperature.
[b] Yield determined in solution by HPLC, using a calibration curve.
[c] Reactions were carried out with 3.3 mmol of **3a**.
[d] Isolated yield after chromatographic purification.

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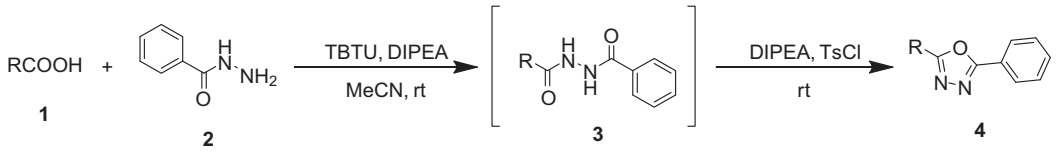
Table 2
Synthesis of 2-aryl-5-phenyl-1,3,4-oxadiazoles[a]



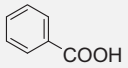
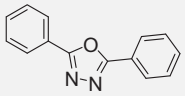
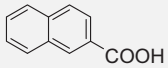
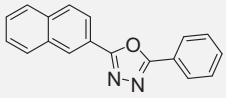
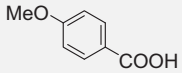
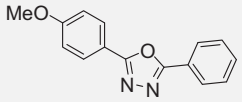
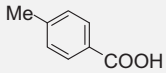
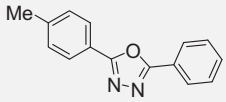
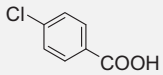
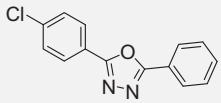
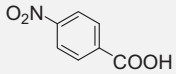
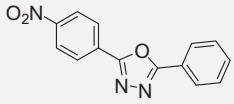
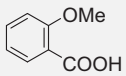
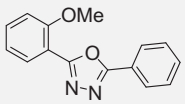
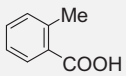
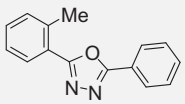
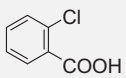
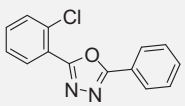
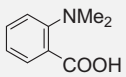
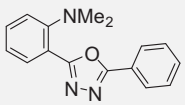
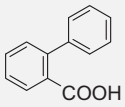
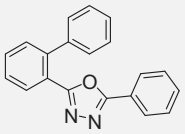
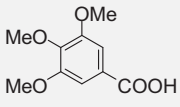
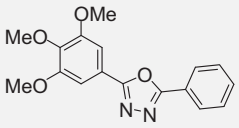
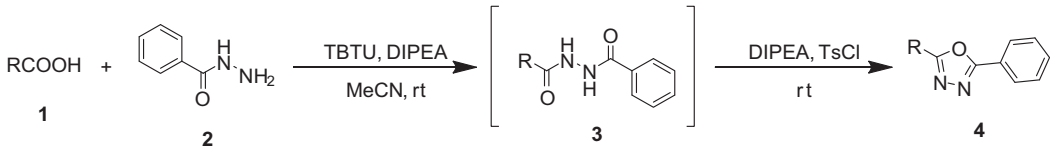
Entry	Carboxylic acid	Product	Yield[b] (%)
1	 **1a**	 **4a**	78
2	 **1b**	 **4b**	79
3	 **1c**	 **4c**	80
4	 **1d**	 **4d**	72
5	 **1e**	 **4e**	74
6	 **1f**	 **4f**	73
7	 **1g**	 **4g**	79
8	 **1h**	 **4h**	63
9	 **1i**	 **4i**	65
10	 **1j**	 **4j**	74

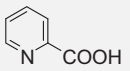
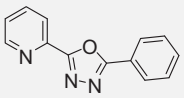
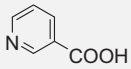
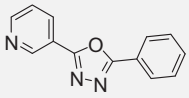
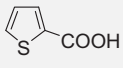
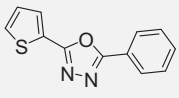
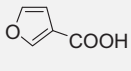
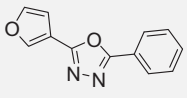
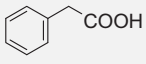
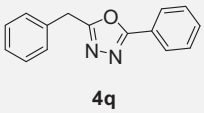
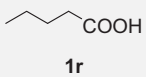
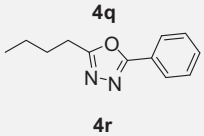
Table 2 (*continued*)

Entry	Carboxylic acid	Product	Yield[b] (%)
11	 **1k**	 **4k**	77
12	 **1l**	 **4l**	81

[a] To a mixture of **1** (5 mmol), **2** (1 equiv), and DIPEA (3 equiv) in MeCN (60 ml) at room temperature was added TBTU (1.1 equiv). To the resulting mixture of the intermediate **3** were then added DIPEA (2 equiv) and TsCl (3 equiv).
[b] Isolated yield.

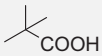
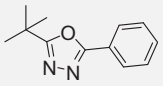
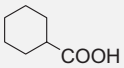
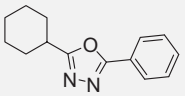
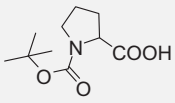
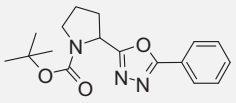
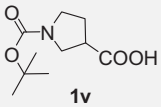
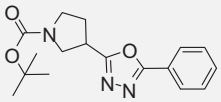
Table 3
Synthesis of 2-heteroaryl-5-phenyl-1,3,4-oxadiazoles and 2-alkyl-5-phenyl-1,3,4-oxadiazoles[a]



Entry	Carboxylic acid	Product	Yield[b] (%)
1	 **1m**	 **4m**	84
2	 **1n**	 **4n**	68
3	 **1o**	 **4o**	79
4	 **1p**	 **4p**	79
5	 **1q**	 **4q**	84
6	 **1r**	 **4r**	75

(*continued on next page*)

Table 3 (*continued*)

Entry	Carboxylic acid	Product	Yield[b] (%)
7	 **1s**	 **4s**	85
8	 **1t**	 **4t**	76
9	 **1u**	 **4u**	90
10	 **1v**	 **4v**	79

[a] To a mixture of **1** (5 mmol), **2** (1 equiv), and DIPEA (3 equiv) in MeCN (60 ml) at room temperature was added TBTU (1.1 equiv). To the resulting mixture of the intermediate **3** were then added DIPEA (2 equiv) and TsCl (3 equiv).
[b] Isolated yield.

In the course of our studies aiming at the optimization of the synthesis of new biologically active chemical entities, we were interested in establishing a convenient, practical, and general methodology for preparing a variety of 2,5-disubstituted-1,3,4-oxadiazoles. The commercial availability of a wide range of carboxylic acids prompted us to investigate the synthesis of 2-phenyl-5-substituted-1,3,4-oxadiazoles via their condensation reaction with benzohydrazide and successive cyclodehydration of the resulting diacylhydrazine intermediates.

As a first instance, we focused on the cyclodehydration reaction of diacylhydrazines. Among the variety of available dehydrating agents, we turned our attention toward 4-methylbenzenesulfonyl chloride (TsCl) because it is a non-toxic and cheap reagent. Thus, benzoic acid, **1a**, was condensed with benzohydrazide, **2**, by using propylphosphonic anhydride (T3P®) as coupling agent to afford the model substrate *N*′-(phenylcarbonyl)benzohydrazide **3a**. Successively, the TsCl-mediated intramolecular cyclocondensation of **3a** was investigated and a solvent/base screening was carried out (Table 1). Both triethylamine (TEA) and K_2CO_3 gave compound **4a** in excellent yield in all the solvents tested (Table 1, entries 1, 5, and 9 and entries 4, 8, and 12, respectively). However, no reaction occurred in the presence of pyridine (Table 1, entries 2, 6, and 10), whilst DBU provided compound **4a** in lower yields (Table 1, entries 3, 7, and 11). Worthy of note is the formation of a by-product identified as *N*,*N*-diethyl-4-methylbenzenesulfonamide, when using TEA as base.

With these satisfactory results in our hands, we started investigating the synthesis of diacylhydrazine derivatives **3** and, in particular, the condensation reaction of a few model carboxylic acids (namely, compounds **1a**, **1b**, **1c,** and **1q**) with benzohydrazide, **2**. Thus, a screening of amide coupling agents, that is, T3P®, *N*,*N*′-dicyclohexylcarbodiimide (DCC), and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), and bases (diisopropylethylamine and triethylamine) in different solvents (dichloromethane, tetrahydrofuran, and acetonitrile) was performed at room temperature. In spite of the fact that T3P® and TBTU provided fast and efficient condensation reactions of 1a-c1a–**c** and **1q** with **2**, isolation of the corresponding diacylhydrazines **3a–c** and **3q** was not always straightforward due to their poor solubility in common solvents. Nonetheless, we speculated that the addition of TsCl to the crude mixtures of compounds **3** could result in the formation of the desired 2-phenyl-5-substituted-1,3,4-oxadiazoles **4**, thus skipping the isolation step of the intermediate diacylhydrazines. We were pleased to find that when using TBTU as the coupling agent, the one-pot protocol furnished very encouraging results. In particular, the best performances were observed when using diisopropylethylamine (DIPEA) as the base in acetonitrile at room temperature, affording the desired compounds **4a–c** (Table 2, entries 1–3) and **4q** (Table 3, entry 5) in satisfactory yields after chromatographic purification.

With this piece of information in our hands, we wished to extend our methodology to a variety of aryl acids **1** (Table 2). Thus, compounds **1** (5 mmol), **2** (1 equiv), and DIPEA (3 equiv) were mixed in MeCN (60 ml) at room temperature and TBTU (1.1 equiv) was added. Once the formation of intermediates **3** reached completeness, more DIPEA (2 equiv) and TsCl (3 equiv) were charged to afford the 2-aryl-5-phenyl-1,3,4-oxadiazoles **4** (Table 2). It should be noted that 1*H*-1,2,3-benzotriazol-1-ol formed during the amide coupling step as a by-product, consumed 1 equiv of TsCl and therefore an excess (3 equiv) of the latter was required to perform efficiently the cyclodehydration step. The crude reaction mixtures were then treated with an aqueous solution of ammonia to transform the excess of TsCl in 4-methylbenzenesulfonamide, thus allowing easier chromatographic purification in the majority of cases (Table 2). However, in a few instances, 4-methylbenzenesulfonamide had to be completely removed prior to the chromatographic purification to obtain pure 1,3,4-oxadiazoles **4**. This was accomplished by treating the crude compounds **4** with a 2 N aqueous solution of NaOH.

As shown in Table 2, both electron-rich and electron-poor aryl carboxylic acids **1a–l** afforded the corresponding 1,3,4-oxadiazoles **4a–l** in good to very good yields. In particular, 4-substituted derivatives **1c–e** reacted more efficiently than the corresponding 2-substituted regioisomers **1g–i**, likely because of the steric hindrance of the *ortho* substituent (Table 2, compare entries 3–5 with entries 7–9).

To further demonstrate the generality of our methodology, we decided to extend it to substrates bearing heteroaryl and alkyl functionalities. Both electron-rich and electron-poor heteroaryl derivatives **1m–p** reacted efficiently under our conditions and the corresponding 2-heteroaryl-5-phenyl-1,3,4-oxadiazoles **4m–p** were prepared in 68–84% yield (Table 3, entries 1–4). Alkanoic acids **1q–t** proved to be excellent substrates as well, affording 1,3,4-oxadiazoles **4q–t** in very good yields (Table 3, entries 5–8). Finally, *N*-Boc-protected α- and β-aminoacids **1u** and **1v** furnished the desired **4u** and **4v** in 90 and 79% yield, respectively (Table 3, entries 9 and 10).

In conclusion, we have developed a mild and efficient one-pot methodology to synthesize a variety of 2-aryl-, 2-heteroaryl-, and 2-alkyl-5-phenyl-1,3,4-oxadiazoles from commercially available carboxylic acids and benzohydrazide. Non-toxic and cheap 4-methylbenzenesulfonyl chloride was employed to convert the 1,2-diacylhydrazine intermediates to the desired 1,3,4-oxadiazoles.

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Supplementary data

Supplementary data (experimental procedures and characterization data for all substrates **4a**–**v**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.139.

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