

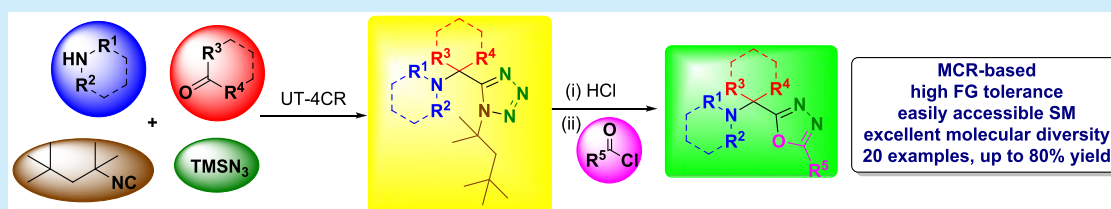
1,3,4-Oxadiazoles by Ugi-Tetrazole and Huisgen Reaction

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Supporting Information



ABSTRACT: Easy to perform, functional group tolerant, and short syntheses of the privileged scaffold oxadiazole are highly desired. Here, a metal-free protocol for MCR-based synthesis of 2,5-disubstituted 1,3,4-oxadiazoles via a Ugi-tetrazole/Huisgen sequence was developed. Optimization and scope and limitations of this short and general sequence are described. The reaction was also successfully performed on a gram scale.

The 1,3,4-oxadiazole skeleton is of considerable interest due to a wide range of biological and pharmacological activities and has been generally recognized as a privileged structure in medicinal chemistry.¹ It has been shown to lower lipophilicity and increase water solubility when introduced into a structure. Oxadiazoles are known as bioisosteres of amides and esters with often superior hydrolytic and metabolic stability, improved pharmacokinetics, and in vivo performance.² Interestingly, oxadiazole peptidic macrocycles showed significantly higher cell membrane penetration compared to their amide congeners.³ They show widespread applications in pharmaceutical chemistry and material science.⁴ Raltegravir,⁵ an antiretroviral drug containing the 1,3,4-oxadiazole moiety for the treatment of HIV infection, is marketed. Several compounds (Figure 1A) are in late-stage clinical trials, including furamizole as an antibiotic agent,⁶ tiadazosin⁷ and nesadipil⁸ for the treatment of hypertension, and zibotentan as an anticancer agent.⁹

Multicomponent reactions (MCRs) are powerful synthetic tools for the synthesis of complex and diverse molecules in a one-pot fashion from more than two starting materials.¹⁰ MCRs are considered green chemistry by reducing the number of synthetic steps, energy consumption, and waste production.¹¹ In the field of MCRs, the Ugi reaction was appealing because four components are combined to a single product in a straightforward one-pot reaction.¹² It is well suited for diversity-oriented synthesis applicable in drug discovery and stands out due to its ease of synthetic operation and functional group tolerability.¹³

Owing to its great importance in multiple areas, several syntheses of the 1,3,4-oxadiazole scaffold are established, including: (1) oxidative cyclization of *N*-acylhydrazones with various oxidizing reagents,¹⁴ (2) cyclodehydration of 1,2-

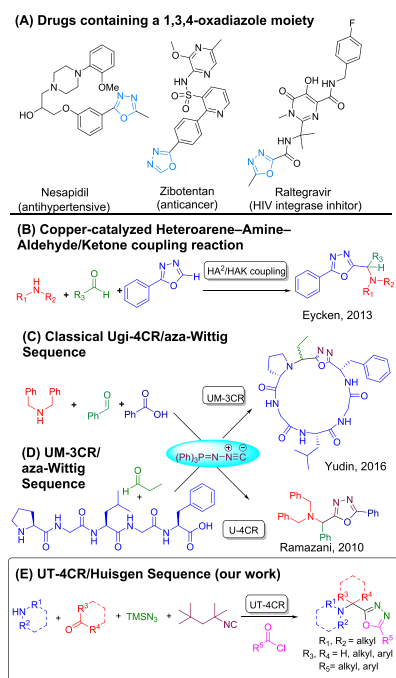


Figure 1. 1,3,4-Oxadiazoles in drugs and synthesis.

diacylhydrazines with dehydrated reagents,¹⁵ (3) direct reaction of carboxylic acids or acyl chlorides with acid hydrazides or hydrazines,¹⁶ (4) C–H activation/Cu-mediated arylation of preformed 2-substituted 1,3,4-oxadiazole,¹⁷ (5)

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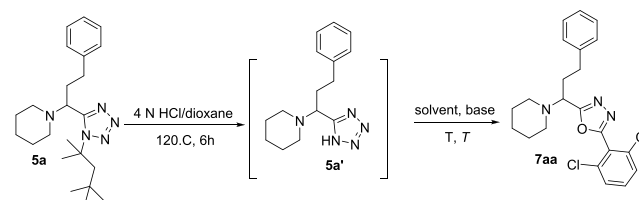
electrophilic substitution of 2-substituted-5-(trimethylsilyl)-1,3,4-oxadiazole toward various electrophiles,¹⁸ (6) oxidative cleavage of the C(sp²)-H or C(sp)-H bond with subsequent cyclization and deacylation,¹⁹ and (7) the Huisgen 1,3,4-oxadiazole synthesis.²⁰ Notably, Ramazani et al. described an MCR approach toward oxadiazoles using (*N*-isocyanimino)-triphenylphosphorane and a Ugi/aza-Wittig sequence (Figure 1C).²¹ Eycken et al. reported a copper-catalyzed direct secondary and tertiary C-H alkylation of azoles through a heteroarene-amine aldehyde/ketone coupling reaction toward 2,5-disubstituted 1,3,4-oxadiazoles (Figure 1B).²² Yudin et al. generated macrocyclic peptides applying Ramazani's method (Figure 1D).³

However, the existing procedures still involve the use of hazardous or expensive reagents, harsh conditions, long reaction times, lack of structural and functional group diversity, or the requirement of linear assembly of reactants using multistep synthesis. Surprisingly, the Huisgen reaction, which can afford 1,3,4-oxadiazoles by the reaction of 5-substituted 1*H*-tetrazoles with electrophiles (such as carboxylic acid anhydrides or acid chlorides), has received comparatively little interest in the past few years.²³ Compared with other methods, the Huisgen reaction is a facile approach to afford the corresponding 2,5-disubstituted 1,3,4-oxadiazoles in a very clean and efficient manner. The convergent approach toward the synthesis of 1,3,4-oxadiazole derivatives with the flexibility to incorporate various substituent groups at both the 2- and 5-positions is thus highly desirable. Thus, we tried to elaborate a convenient method for constructing diversely 2,5-substituted 1,3,4-oxadiazoles from easily accessible starting materials via Ugi/Huisgen sequence reactions.

To test our hypothesis and design, piperidine **1a** (1 equiv) was reacted with 3-phenylpropanal **2a** (1 equiv), trimethylsilyl azide **3** (1.1 equiv) and *tert*-octyl isocyanide **4** (1.1 equiv) in methanol (room temperature, 12 h) to obtain the Ugi product **5a** in very good yield (85%). Then **5a** was treated with 4 N HCl/dioxane to deprotect the *tert*-octyl group and to give 1-(3-phenyl-1-(1*H*-tetrazol-5-yl)propyl)piperidine **5a'**. This intermediate tetrazole **5a'** was directly dissolved in pyridine (0.5 M) and was treated with 2,6-dichlorobenzoyl chloride **6a** (1.0 equiv) at 100 °C for 6 h. This reaction afforded the desired oxadiazole product (**7aa**) in 30% yield (Table 1, entry 1) and motivated us to optimize the conditions. Regarding the isocyanide component, we chose cleavable isocyanides that are high yielding in the first step of the Ugi tetrazole reaction. After this first successful attempt for the 1,3,4-oxadiazole synthesis, the same procedure was repeated using the *tert*-butyl isocyanide, as an alternative cleavable isocyanide that in theory could result in better atom economy. Although the Ugi tetrazole product was obtained in very good yield, similarly to the previous time, the second step to deprotect the *tert*-butyl group turned out to be much more challenging. Therefore, in the first two reaction steps, the *tert*-octyl isocyanide gave a better outcome and was used in the optimization and investigation of the reaction scope.

Careful variation of conditions and analysis revealed that conversion of the tetrazole was not quantitative. In light of this, the ratio of the reactants **5a'** and **6a** was increased to 1:1.2, which enhanced the yield of **7aa** to 38% (Table 1, entry 2). After prolonging the reaction time to 8 h and increasing the reaction temperature to 110 °C, **7aa** was obtained in 44% yield (entry 3). A higher reaction temperature gave a slightly better yield (entry 4). Increasing the amount of solvent reduced the

Table 1. Optimization Studies for the Formation of **7aa**^{a,b}



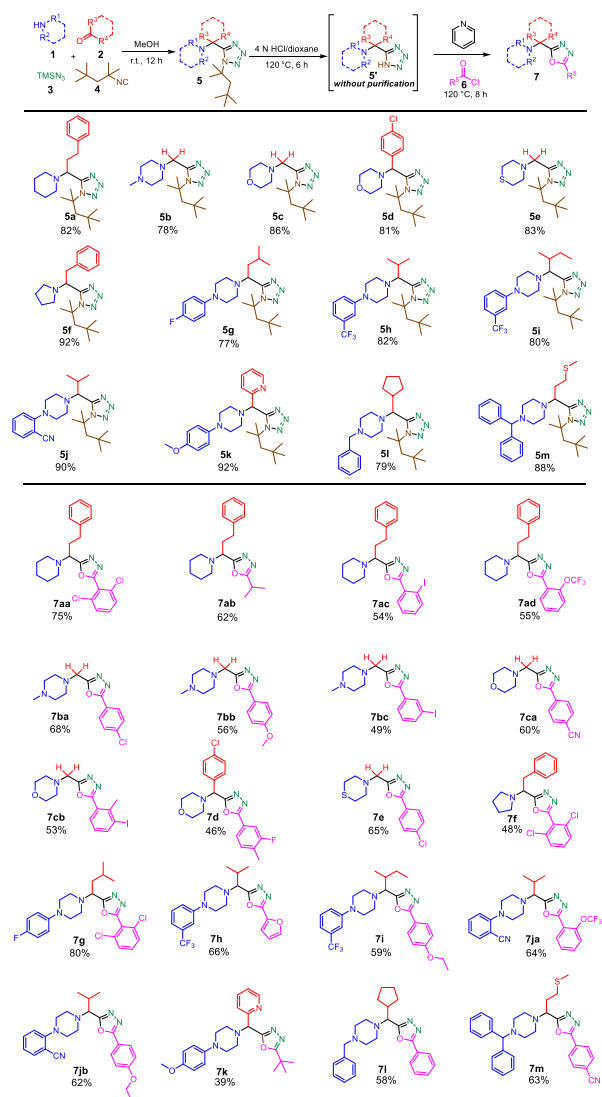
entry	2,6-dichloroPhCOCl (equiv)	solvent (v/v)	time (h)	T (°C)	yield (%)
1	1.0	pyr	6	100	30
2	1.2	pyr	6	100	38
3	1.2	pyr	8	110	44
4	1.2	pyr	8	120	50
5 ^c	1.2	pyr	8	120	45
6	1.5	pyr	8	120	75
7	1.5	pyr	10	120	70
8	1.5	pyr	12	120	69
9	2.0	pyr	8	120	65
10	1.5	pyr	8	140	61
11	1.5	pyr	8	160	60
12	1.5	pyr/MeCN (1:1)	8	120	25
13	1.5	pyr/MeCN (1:2)	8	120	21
14	1.5	pyr/MeCN (1:3)	8	120	20

^aThe Ugi reaction was carried out using **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (1.1 mmol), and **4** (1.1 mmol) in MeOH (1 M) for 12 h at rt. ^bReaction conditions: **5a'** (0.5 mmol), solvent (1 mL), isolated yields. ^cReaction mixture concentration (0.25 M).

yield (entry 5). Surprisingly, increasing the amount of **6a** to 1.5 equiv considerably improved the reaction performance (75% yield; entry 6). Increasing the reaction time did not help improve the outcome of the product (entries 7 and 8), which was the same case as increasing the number of equivalents of acyl chloride **6a** (entry 9). However, increasing the temperature to 140 and 160 °C resulted in lower yields (entries 10 and 11). Furthermore, the outcome of the reaction was sharply decreased by applying a mixture of pyridine and acetonitrile as cosolvents in different ratios (entries 12–14). Thus, the best conditions for the Huisgen reaction were determined to be 1.0 equiv of 5-substituted-1*H*-tetrazole and 1.5 equiv of acyl chloride in 0.5 M of pyridine at 120 °C for 8 h.

With the optimized conditions in hand, a series of Ugi products (**5a**–**5m**) were synthesized in good to excellent yield and were used to explore the scope and limitations of the Huisgen reaction by reacting diverse secondary amines with different aldehydes/ketones, *tert*-octyl isocyanide, and TMSN₃ in methanol followed by deprotection and Huisgen rearrangement to furnish the corresponding library **7a**–**m** (Scheme 1). Surprisingly, all of the substrates **1**, **2**, **3**, **4**, and **6** led to the expected 1,3,4-oxadiazole products **7a**–**m** in 39–80% yields via three steps, almost irrespective of the electronic and steric factors of the substituents present, indicating great functional group tolerance. As shown in Scheme 1, various aliphatic aldehydes including 3-phenylpropanal, formaldehyde, 2-phenylacetaldehyde, 3-methylbutanal, isobutyraldehyde, 2-methylbutanal, cyclopentanecarbaldehyde, and 3-(methylthio)propanal proceeded well in this MCR and Huisgen reaction, which is not easily achieved in reported work.^{3,21,22} An aromatic aldehyde with a substituted group chloro was

Scheme 1. Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles 7a–d



^aThe amine, aldehyde, azide, isocyanide, and aryl chloride components are depicted with blue, red, brown, green, and pink color, respectively. ^bThe Ugi reaction was carried out using **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.1 mmol), and **4** (1.1 mmol) in MeOH (1 M) for 12 h at rt. ^cReaction conditions: **5** (0.5 mmol), 4 N HCl/dioxane (1 mL), 120 °C, 6 h; then **6** (0.75 mmol), pyridine (1 mL), 120 °C, 8 h. ^dYield refers to the purified products.

tolerated (**7d**), and heterocyclic aldehyde with the scaffold of pyridine was compatible in this process to deliver the products in good yields (**7k**).

Meanwhile, a variety of secondary amines were also subjected to this process. Interesting moieties often used to enhance water solubility of compounds, such as piperidine, 1-methylpiperazine, morpholine, thiomorpholine, and pyrrolidine, participate in this MCR smoothly to produce the products in moderate to good yields (**7a–f**). Besides, 1-phenylpiperazine containing valuable functional groups such as fluoro, trifluoromethyl, cyano, and methoxy were also applied and gave the corresponding products in good yields (**7g–k**). Similarly, 1-benzylpiperazine and 1-benzhydrylpiperazine also furnished the different 1,3,4-oxadiazole products by 58% and 63% yields, respectively. Finally, the scope of aryl chlorides was

also tested. These diverse aryl chlorides could well engage in this Ugi/Huisgen sequence reactions to treat with tetrazoles for rapid entry to functionalized 1,3,4-oxadiazoles in moderate to good yields (**7a–m**). The fluoro, chloro, iodo, methoxy, ethoxy, and cyano were also compatible, and these functional groups could offer ample opportunity for late-stage derivatization. In addition, benzoyl chloride, isobutyryl chloride, pivaloyl chloride and heterocyclic aryl chloride based on furan were well applicable in this methodology to furnish the corresponding products in good yields (**7l**, **7ab**, **7k**, **7h**).

Compound **7e** has been confirmed by X-ray single-crystal analyses (Figure 2 and Supporting Information). Both the 1,3,4-oxadiazole and *p*-chlorophenyl rings are flat and coplanar and form π – π stacking motifs in the crystal (Figure 2).

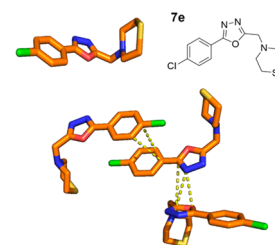
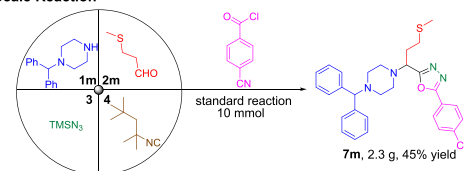


Figure 2. X-ray structure of compound **7e** (CCDC 1942923).

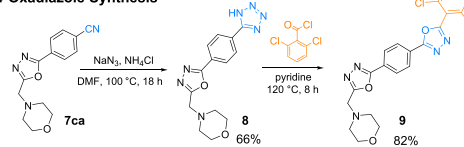
Furthermore, the scalability of this method was investigated (Scheme 2A). A four-component reaction of amine **1m**,

Scheme 2. Gram-Scale Reaction and Synthetic Application

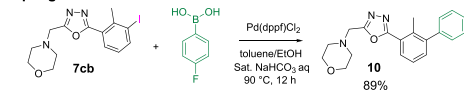
(A) Gram-Scale Reaction



(B) Bis-1,3,4-Oxadiazole Synthesis



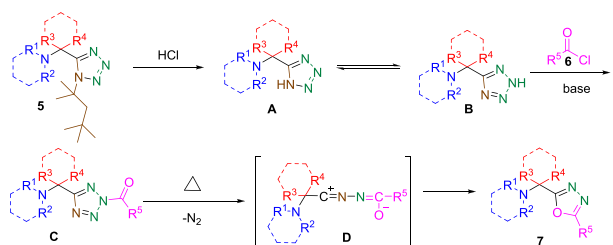
(C) Suzuki Coupling



aldehyde **2m**, TMSN_3 **3**, and *tert*-octyl isocyanide **4** was conducted in 10 mmol scale, further reacting with 4-cyanobenzoyl chloride, while the 1,3,4-oxadiazole product **7m** could be obtained in 45% yield (2.3 g). Lastly, we showed several synthetic applications of the herein described oxadiazoles. Product **7ca** was reacted with sodium azide to afford tetrazole **8**, which was further treated with 2,6-dichlorobenzoyl chloride to deliver unsymmetrical bis-oxadiazole **9** (Scheme 2B). In another application, the iodo group of **7cb** was coupled with (4-fluorophenyl)boronic acid to give the derivate **10** by a Suzuki reaction (Scheme 2C).

A plausible mechanism is shown in Scheme 3. The deprotection of the *tert*-octyl group under acidic condition gives the monosubstituted tetrazole (intermediate A), which is

Scheme 3. Proposed Reaction Mechanism



N-acylated by the corresponding acyl chloride (intermediate C). The unstable *N*-acylated tetrazole undergoes the Huisgen rearrangement with nitrogen elimination, ring-opening (intermediate D), and final cyclization toward the 1,3,4-oxadiazole (7).

In summary, an MCR-based synthesis of 2-fold substituted 1,3,4-oxadiazoles has been developed. Considering the importance of 1,3,4-oxadiazole derivatives in natural products and drug discovery, this method provides simple and distinct access to these molecules from rapidly accessible starting materials. Diversity can be achieved through the secondary amine, the aldehyde, and the aryl chloride components. This protocol offers a rapid approach to the 1,3,4-oxadiazole scaffold, along with the achievement of remarkable structural diversity and brevity. The process uses readily available starting materials and simple operation, provides good scalability, and will therefore become a synthetic useful method in organic synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.9b02614](https://doi.org/10.1021/acs.orglett.9b02614).

Experiment procedures, compound data, NMR spectra, HRMS, and crystal structure determinations (PDF)

Accession Codes

CCDC 1942923 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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