ACS Combinatorial Science

Review

Cite This: ACS Comb. Sci. 2018, 20, 309−329

pubs.acs.org/acscombsci

Current Parallel Solid-Phase Synthesis of Drug-like Oxadiazole and Thiadiazole Derivatives for Combinatorial Chemistry

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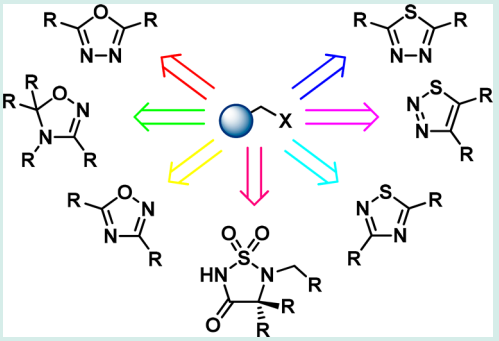
ABSTRACT: Solid-phase organic synthesis is a powerful tool in the synthesis of small organic molecules and building of libraries of compounds for drug discovery. Heterocyclic compounds are important components of the drug discovery field as well and serve as a core for hundreds of marketed drugs. In particular, oxadiazole and thiadiazole cores are compounds of great interest due to their comprehensive biological activities and structural features. Therefore, a plethora of oxadiazole and thiadiazole synthesis methodologies have been reported to date, including solution and solid-phase synthesis methodologies. In this review, we concentrate on and summarize solid-phase synthetic approaches of the oxadiazole and thiadiazole derivatives.



KEYWORDS: *oxadiazole, thiadiazole, solid-phase synthesis, parallel synthesis, combinatorial chemistry, drug design*

INTRODUCTION

Heterocyclic compounds are one of the largest classes of organic compounds and play an important role in medicinal chemistry and drug synthesis. Heterocycles are widely used in the field of medicinal chemistry and are frequently found in a large percent of biomolecules, such as proteins, vitamins, and natural products. The majority of biologically active compounds, including antifungal, anti-inflammatory, antibacterial, antioxidant, anticancer activity, insecticidal agents, and other activities, contain heterocyclic compounds.[1,2]

Among heterocyclic compounds, oxadiazoles and thiadiazoles have shown high potential as therapeutic agents against various diseases. Both oxadiazole and thiadiazole have a five-membered ring system containing an oxygen or sulfur atom, two nitrogen atoms, and two double bonds, providing an aromatic system that exhibits a wide variety of biological activities. Although oxadiazole and thiadiazole have four isomers each (Figure 1), the 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives are attracting more interest and thus have more reports on synthesis methodologies as well as on biological studies.

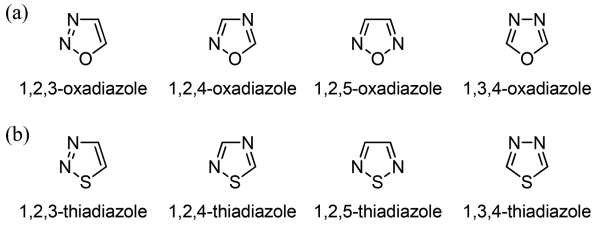


Figure 1. Isomers of (a) oxadiazole and (b) thiadiazole.

In recent years, several reviews of synthetic approaches and pharmacological activities of oxadiazoles and thiadiazoles have been published.[3−19] Additionally, our research group reviewed the solid-phase synthesis of five-membered ring heterocycles using carbon disulfide, where we mentioned the solid-phase synthesis of 1,3,4-oxadiazoles and 1,2,4- and 1,3,4-thiadiazoles.[20] In this review, we concentrate on the solid-phase synthesis reports of oxadiazoles and thiadiazoles and look more closely at the 1,3,4-oxadiazoles and 1,3,4-thiadiazoles due to their peculiar properties.

Oxadiazoles and thiadiazoles are privileged structure class compounds that demonstrate widespread pharmacological activities, such as anticancer,[21] antiviral,[22] anti-inflammatory,[23] antimicrobial,[24] anticonvulsant,[25] cardiovascular,[26] antimalarial,[27] antidiabetic,[28] and antitubercular[29] activity, against Alzheimer's disease,[30] obesity,[31] and so forth.[32] Moreover, oxadiazoles and thiadiazoles are also attractive scaffolds because of their bioisosteric abilities to replace carboxylic acids, esters and carboxamides, and other structural motifs.

Additionally, there are several drugs that contain 1,3,4-oxadiazoles, the most studied isomer, such as the antiretroviral drug against HIV, raltegravir,[33] anticancer agent zibotentan,[34] antibiotic drug furamizol, tiodazosin, and nesapidil as antihypertensive drugs (Figure 2).[3,8] Drugs containing 1,2,4-oxadiazoles also have various activities, such as oxolamine with antitussive and anti-inflammatory activity, irrigor with anesthetic and vasodilator activity, and libexin with antitussive activity (Figure 2).[4c] Several drugs on clinical studies contain 1,3,4-thiadiazole scaffolds: acetazolamide, methazolamide,

Received: March 27, 2018
Revised: April 26, 2018
Published: May 1, 2018

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

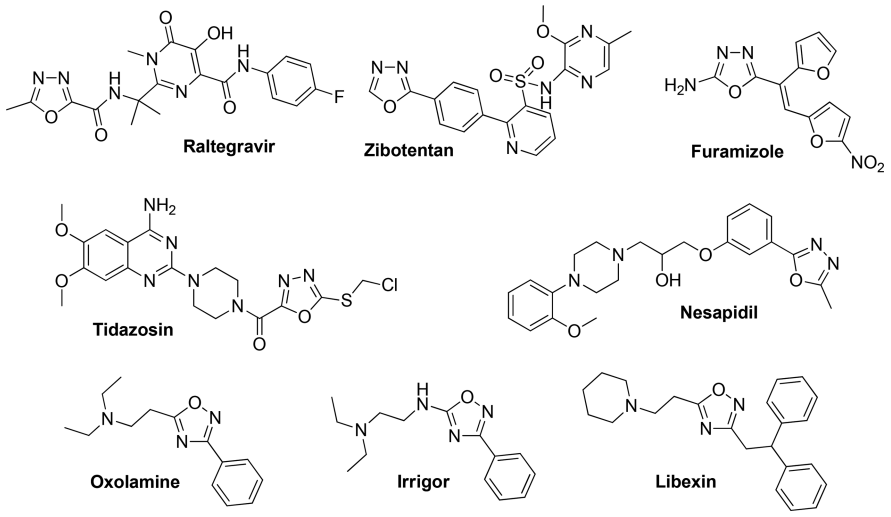


Figure 2. Drugs containing an oxadiazole core.

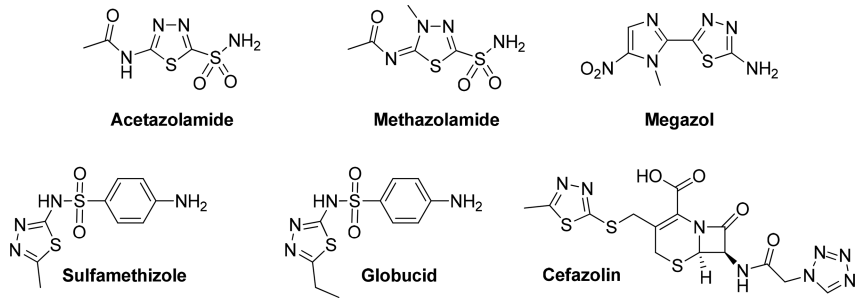
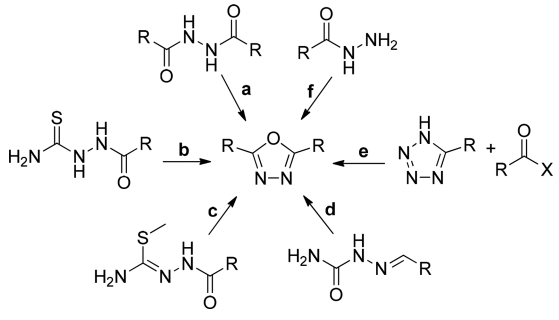


Figure 3. Drugs containing a 1,3,4-thiadiazole core.

megazol, sulfamethizole, and globucid; however, among them, cefazolin is the only commercial drug (Figure 3).[10,21f,35,36]

1. Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles. *1.1. Recent Solution-Phase Synthesis Methodologies of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles.* The general 1,3,4-oxadiazole solution synthesis methods reported in the literature can be classified into four categories: (i) dehydrative cyclization of semicarbazides using dehydrating agents such as $POCl_3$, $SOCl_2$, concentrated H_2SO_4, the Burgess reagent, Appel conditions, and phosphonium reagents (Scheme 1, routes **a**, **c**, and **d**); (ii) oxidative desulfurization of thiosemicarbazides using I_2/NaOH, *p*-tosyl chloride (*p*-TsCl), methyl iodide, ethyl bromoacetate, carbodiimides, mercuric salt, and lead oxide (Scheme 1, route **b**); (iii) Huisgen reactions of tetrazoles and acid chlorides (Scheme 1, route **e**); and (iv) one pot procedures involving compounds bearing nitrogen atoms (i.e., hydrazides) and another reagent that constitutes the 5-substituent source such as CS_2, carboxylic acids, and isothiocyanates (Scheme 1, route **f**).[5,6,29a,37−46]

Scheme 1. Synthesis of 2,5-Disubstituted-1,3,4-oxadiazoles



As for the recently reported solution-phase synthetic approaches, researchers concentrated on the improvement of the classic methodologies together with the use of less hazardous reagents and harsh conditions, eco-friendly techniques, and reduction of the overall step number and/or reaction time. Accordingly, Tokumaru et al. reported the synthesis of 1,3,4-oxadiazoles from acyl hydrazides under semiaqueous conditions with good isolated yields of the products. In this approach, 1,3,4-oxadiazoles were synthesized by coupling of *α*-bromo nitroalkanes with acyl hydrazides to yield the 2,5-disubstituted oxadiazole directly, avoiding a 1,2-diacyl hydrazide intermediate in the presence of water with mildly basic reaction conditions.[47]

Gnanasekaran et al. reported a new approach to the synthesis of 2-substituted and 2,5-disubstituted 1,3,4-oxadiazoles from arylhydrazides and orthoesters using catalytic NH_4Cl. The optimized reaction is performed using 30 mol % of NH_4Cl in 100% EtOH and is generally complete within 1 h for nonaromatic orthoesters and 2−10 h for aromatic orthoesters with high yields and minimal purification required.[48]

Ji et al. developed a novel palladium-catalyzed oxidative annulation reaction for the C−O and C−N bond formations for the direct construction of 1,3,4-oxadiazole-2(3*H*)-ones. Carbon monoxide (CO) was used as a carbon atom source for the oxidative carbonylation of benzohydrazides. The use of $Pd(TFA)_2$ as a catalyst with the addition of 1.5 eq of CuO in the presence of CH_3CN and TFA afforded the desired products

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

in good yields.[49] On the other hand, Gao et al. reported direct annulation of hydrazides to 1,3,4-oxadiazoles through oxidative C(CO)−C(methyl) bond cleavage of methyl ketones. The reaction was accomplished with the methyl ketones reacting with hydrazides in the presence of I_2 and K_2CO_3.[50]

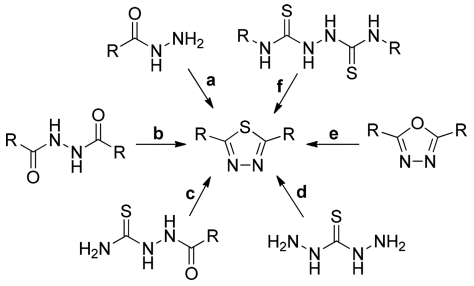
Wang et al. developed an upgraded Huisgen reaction of tetrazoles by replacing acid chlorides with aryl aldehydes. A metal- and base-free one-pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles via a radical-promoted cross-dehydrogenative coupling of tetrazoles and aryl aldehydes with di-*tert*-butyl peroxide as an oxidant, followed by thermal rearrangement, generated the desired products in moderate-to-good yields.[51]

Jasiak et al. reported the synthesis of 5-aryl-2-(2-arylethenyl)-1,3,4-oxadiazoles via oxidative cyclization of *N*-aroylhydrazones by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant. Two synthetic approaches were presented: (i) stepwise reaction with the *N*-aroylhydrazones as intermediates with further cyclization under DDQ and (ii) one-pot synthesis with the addition of *p*-TsCl to complete cyclization. Both pathways were conducted with the reflux of toluene for 2−10 h.[52]

Several research groups reported oxidative desulfurization using iodine-containing reagents. Patel et al. reported the oxidative desulfurization approach using iodobenzene and Oxone with Et_3N at room temperature (rt).[53] Meanwhile, Chang et al. reported a transition-metal-free oxidative cyclization of acylhydrazones into 1,3,4-oxadiazoles by employing stoichiometric molecular iodine in the presence of K_2CO_3.[54] Furthermore, they developed this methodology for the synthesis of 2-amino-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. The 2-amino-1,3,4-oxadiazoles were synthesized by the condensation of benzaldehydes and aminourea hydrochloride, and 2-amino-1,3,4-thiadiazoles were prepared via the condensation of aldehydes with thiosemicarbazides. Reactions were conducted in the presence of iodine and K_2CO_3 with 1,4-dioxane at 80 °C.[55] In addition, Chaudhari et al. used *o*-iodoxybenzoic acid (IBX) as a desulfurative agent for the synthesis of 2-amino-1,3,4-oxadiazoles and 2,5-diamino-1,3,4-thiadiazoles. They used the IBX/TEA system with CH_2Cl_2 at 0 °C, and the reactions were completed within 10 min, accommodating the desired products in high yields (>84%).[56]

In the case of 1,3,4-thiadiazoles, there are three main synthetic approaches, such as (i) from acyl hydrazides (from acid hydrazides[57,58] and diacylhydrazides,[59] Scheme 2, routes **a** and **b**); (ii) cyclization of thiohydrazines and its derivatives (thiosemicarbazides,[60,61] thiocarbazides,[62,63] dithiocarbazates,[64] thiohydrazides,[65] bithioureas;[66] Scheme 2, routes **c**, **d**, and **f**); and (iii) from 1,3,4-oxadiazoles,[67] by replacement of the oxygen atom by the sulfur atom (Scheme 2, route **e**). More detailed overviews of the solution-phase 1,3,4-thiadiazole synthesis methodologies are well-provided in the previously reported reviews.[11,13,18]

Scheme 2. Synthesis of 2,5-Disubstituted-1,3,4-thiadiazoles



1.2. Solid-Phase Synthesis Methodologies of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles. Solid-phase organic synthesis (SPOS) is a powerful tool in the synthesis of small druglike molecules that facilitates the synthetic process and accommodates rapid access to the libraries of compounds. Various research groups have reported the solid-phase synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles for the past few years. Below, we provide a detailed review of the reported papers.

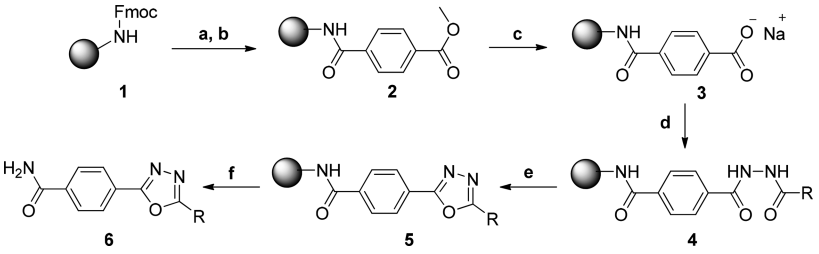
The 1,3,4-oxadiazoles were mainly synthesized via dehydrative cyclization from acylhydrazine/acylhydrazide and thiosemicarbazide intermediates on solid phase. Because the reactions were accomplished mainly under basic conditions, the acid-labile linkers were preferable. One of the first reports was presented by Brown et al., who reported on the solid-phase synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from resin-bound 1,2-diacylhydrazines 1,3-diisopropyl carbodiimide (DIC) as a dehydrative agent.[68] Acid-sensitive Rink resin was used as a solid support. Scheme 3 shows the details. First, the monomethyl terephthalate was attached to the Fmoc-deprotected Rink resin **1** in the presence of benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and *N*,*N*-diisopropylethylamine (DIPEA), resulting in methyl ester **2**. Methyl ester **2** was then subjected to basic hydrolysis and formed carboxylate anion **3**, which was coupled with appropriate acylhydrazines to give the required 1,2-diacylhydrazines **4**. Heating intermediate **4** in the presence of the DIC and *N*,*N*-dimethylformamide (DMF) and subsequent cleavage from the solid support with trifluoroacetic acid (TFA) in dimethyl chloride (DCM) resulted in the 2,5-disubstituted 1,3,4-oxadiazoles **6** with good yield (>60%, 6-step overall yield) and purity (>71%).

Liu et al. also reported the solid-phase synthesis of the 2,5-disubstituted 1,3,4-oxadiazoles from acylhydrazines (Scheme 4).[69] However, their synthetic strategy was based on the treatment of acylhydrazines with CS_2 and KOH to afford 1,3,4-oxadiazole derivatives. Merrifield resin **7** was converted to methyl ester resin **8** by treatment of the excess of methyl 4-hydroxybenzoate. Resin **8** was treated with hydrazine hydrate in the presence of hexamethylphosphoramide (HMPA) at 90 °C for 24 h to afford resin-bound acylhydrazine **9**. Intermediate **9** was then cyclized to 2-mercapto-1,3,4-oxadiazole resin **10** with CS_2 and KOH at reflux for 8 h. Further reaction of resin **10** with various electrophiles (RX) in the presence of NaOH gave corresponding resin **11**. The 1,3,4-oxadiazoline-5-thione derivatives **12** were obtained after cleavage using 10% TFA in DCM. The products resulted in 78−88% 5-step overall yield and high purity (>81%).

Cesarini et al.[70] developed the 1,3,4-oxadiazole formation through the traceless release from the solid support with acylhydrazide intermediates. The *o*-methoxybenzyl linker attached to the polystyrene resin via a flexible 4-butyryloxy spacer was used for the synthesis (Scheme 5). Cesarini et al. attached 2-acylhydrazides on resin **13**, and the formed acylhydrazones **14** were reduced to hydrazides **15** using a borane−pyridine complex. The acylation of resin **15** with anhydrides and pentafluorophenyl esters in the presence of *N*-methylimidazole (NMI) afforded 2-acylhydrazides **16**. The last step, the dehydrative cyclative release of the 1,3,4-oxadiazoles to form resin **16**, was performed under trifluoroacetic anhydride (TFAA), TFA, and DCM (20:75:5) cleavage cocktail, affording

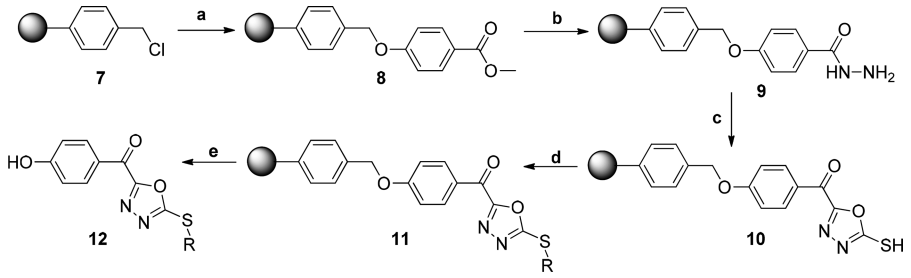
DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 3. Solid-Phase Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles Using DIPCDI[a]



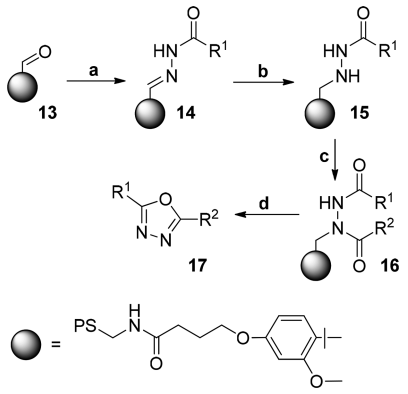
[a]Reaction conditions: (a) 20% piperidine in DMF; (b) monomethyl terephthalate, PyBOP, DIPEA, DMF; (c) 2 M NaOH, THF(aq); (d) $RCONHNH_2$, PyBOP, DIPEA, DMF; (e) DIC, DMF, 100 °C, 18 h; (f) TFA:DCM (1:1).

Scheme 4. Solid-Phase Synthesis of 1,3,4-Oxadiazoline-5-thione Derivatives[a]



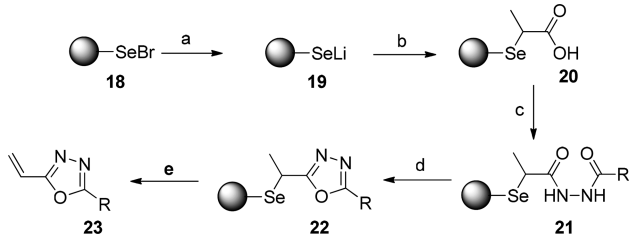
[a]Reaction conditions: (a) methyl 4-hydroxybenzoate, DMF, 24 h; (b) $NH_2NH_2{\cdot}xH_2O$, HMPA, 90 °C, 24 h; (c) (i) CS_2, KOH, EtOH, 8 h; (ii) 3 M HCl; (d) RX, NaOH (aq), EtOH, 4.5 h; (e) 10% TFA in DCM, 1 h.

Scheme 5. 1,3,4-Oxadiazole Formation on Solid Phase via Cyclative Release[a]



[a]Reaction conditions: (a) 2-acylhydrazides, AcOH, DCM, 24 h; (b) DCM/AcOH/pyridine·BH_3 (85:10:5), 8 h; (c) anhydrides or pentafluorophenyl esters, NMI, DCM, 2 days; (d) TFAA/DCM/TFA (20:75:5), 5 h.

Scheme 6. Solid-Phase Synthesis of the Route of Vinyl-Substituted 1,3,4-Oxadiazoles from Polymer-Supported α-Selenopropionic Acid[a]



[a]Reaction conditions: (a) $LiBH_4$, THF, 1 h; (b) 2-bromopropionic acid, 6 h; (c) $RCONHNH_2$, DMC, Et_3N, DCM, 24 h; (d) $POCl_3$, reflux, 12 h; (e) H_2O_2, THF, 1.5 h.

desired products **17**. All reactions were run at rt. Additionally, the research group demonstrated the role of TFAA in the process.

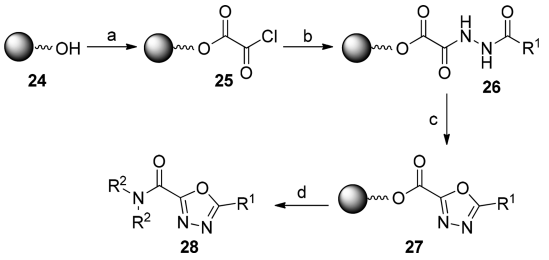
Unlike other research groups, Fu et al. used polystyrene-supported α-selenopropionic acid for the synthesis of the 1,3,4-oxadiazoles (Scheme 6).[71] Polymer-supported α-selenopropionic acid **20** was prepared by the treatment of a THF-swollen suspension of polystyrene-bound selenium bromide **18** with $LiBH_4$ followed by treatment with 2-bromopropionic acid. For the next step, the diacylhydrazination reaction, they used 2-chloro-1,3-dimethylimidazolinium chloride (DMC) for the coupling of the resin with the attached α-selenopropionic acid **20** and aromatic hydrazides, affording diacylhydrazide resin **21**. The intermediate resin **21** was converted to 1,3,4-oxadiazole by cyclative dehydration with $POCl_3$ as a dehydrative agent. The following *syn*-elimination of the selenoxide with excess of 30% hydrogen peroxide resulted in the vinyl-substituted 1,3,4-oxadiazole derivatives with moderate to good yield (74−81%, 5-step overall yield) and high purity (>90%).

Synthesis of the 2-amido-1,3,4-oxadiazoles was developed by Korbard et al. using hydroxypentyl *Jandajel* polymer support with attached oxalyl chloride.[72] The hydroxy-functionalized *Jandajel* **24** was treated with excess of the oxalyl chloride in the presence of DCM at rt for 2 h to give 2-chloro-2-oxoacetate resin **25**. Resin **25** was treated with a series of *N*-acylhydrazides ($R^1CONHNH_2$) in *N*-methyl-2-pyrrolidone (NMP) using *N*-methylmorpholine (NMM) as a base to provide the resin-bound linear precursor 2-(*N*-acylhydrazino)-2-oxoacetate **26**. The intramolecular dehydrative cyclization of intermediate **26** was performed using the classic dehydrative agent $POCl_3$ with heating for 3 h, which resulted in the polymer-supported 1,3,4-oxadiazoles **27**. Finally, the desired products **28** were obtained

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

by trimethylaluminum-mediated smart cleavage of 1,3,4-oxadiazole **27** from the polymer support with further purification. The 2-amido-1,3,4-oxadiazoles were obtained in good yields (36−67%, 4-step overall yield). Scheme 7 shows the detailed synthetic route.

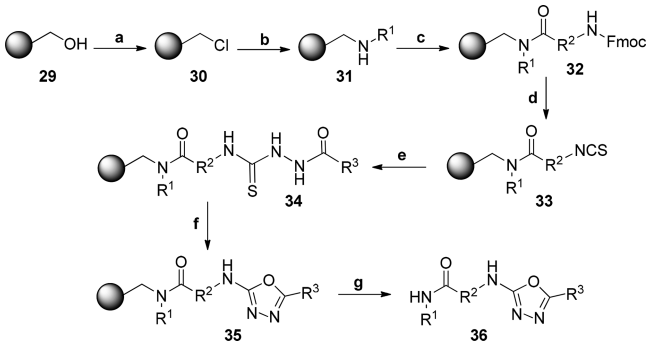
Scheme 7. Solid-Phase Synthesis of the 2-Amido-1,3,4-oxadiazoles via *JandaJel*[a]



[a]Reaction conditions: (a) oxalyl chloride, DCM, rt, 2 h; (b) $R^1CONHNH_2$, NMP:NMM (3:1), 2 h; (c) $POCl_3$, 130 °C, 3 h; (d) amines, $AlMe_3$, toluene, 0−50 °C, 2−3 h.

Another attractive intermediate for the solid-phase synthesis of the 1,3,4-oxadiazoles, as well as the synthesis of the 1,3,4-thiadiazoles, is the thiosemicarbazide. The thiosemicarbazides can be treated with dehydrative or desulfurative agents to selectively give 1,3,4-oxadiazole or 1,3,4-thiadiazole derivatives. Kilburn et al. provided the earliest solid-phase reports with thiosemicarbazide as an intermediate (Scheme 8).[73] They

Scheme 8. Solid-Phase Synthesis of 1,3,4-Oxadiazoles Using SASRIN Resin and EDC·HCl[a]



[a]Reaction conditions: (a) Ph_3P, C_2Cl_6, THF (dry), 6 h; (b) R^1NH_2, NMP, 16 h; (c) $HOOCR^2NHFmoc$, PyBrOP, DIPEA, NMP, 4 h; (d) (i) piperidine:NMP (1:4), 20 min; (ii) di(2-pyridyl)thiocarbonate, DCM, 2 h; (e) $R^3CONHNH_2$, NMP, 16 h; (f) EDC·HCl, DMSO, 80 °C, 16 h; (g) TFA:DCM (1:1), 1 h.

reported the formation of 1,3,4-oxadiazole via the cyclo-desulfuration of acyl thiosemicarbazides. The SASRIN resin was used as a polymer support. SASRIN resin **29** was first converted to chloromethyl analogue **30** using triphenylphosphonium dichloride, and then the chloride-containing resin **30** was substituted with different amines. The polymer-supported amines **31** were coupled with the appropriate amino acids. The following treatment with di(2-pyridyl)-thionocarbonate affords isothiocyanate **33**, which is subsequently condensed with the acid hydrazides to give the acyl thiosemicarbazide intermediates **34**. The cyclization of resin **34** was run by treatment with (3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) at 80 °C for 16 h. The cleavage of product **36** from resin **35** was afforded by treatment with 50% TFA in DCM.

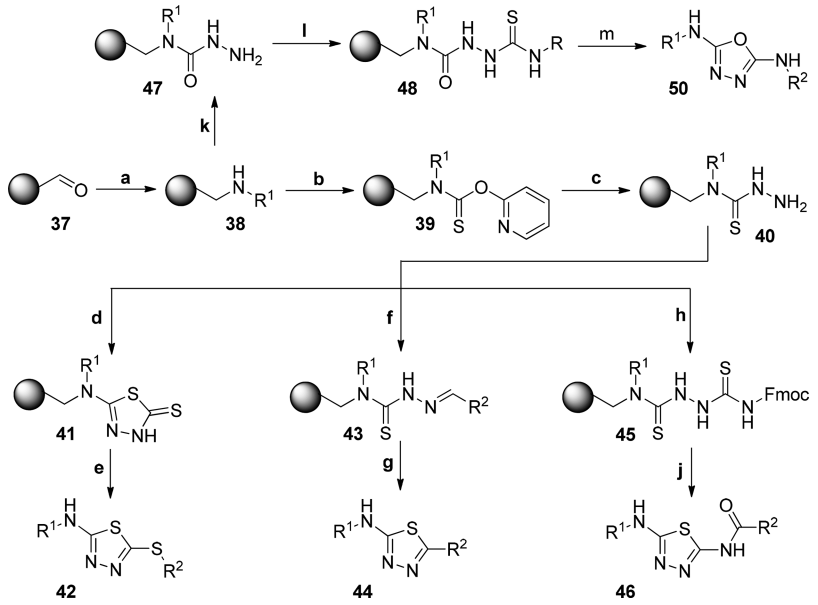
The Severinsen et al. group developed four new versatile solid-phase synthesis protocols for the preparation of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles using thiosemicarbazide intermediates.[74] The commercially available 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene **37** was treated with various primary amines under standard reductive amination conditions to yield the respective resin-bound benzyl amine derivates **38** as shown in Scheme 9. Benzyl amine resin **38** reacted with di(2-pyridyl)-thionocarbonate (DPT) to give isothiocyanate **39** that was converted to thiosemicarbazide resin **40** using hydrazine hydrate in dimethyl sulfoxide (DMSO) at 50 °C. Thiosemicarbazide resin **40** served as a versatile intermediate, and treatment with different reagents resulted in the diverse 1,3,4-thiadiazole derivatives. First, thiosemicarbazide resin **40** was converted to thione resin **41** using DPT in DCM. Thione resin **41** was reacted with numerous alkylating agents to accomplish S-alkylation with the following cleavage with TFA and DCM to give 2-alkylthio-5-alkylamino-1,3,4-thiadiazoles **42**. Next, the thiosemicarbazide resin **40** was converted to imine resin **43** by reacting with aldehydes in the presence of trimethyl orthoformate (TMOF) and NMP. Cyclization of imine resin **43** was performed by treatment with $FeCl_3$ in DCM/MeOH and, following cleavage with TFA in DCM, yielded 5-alkyl-1,3,4-thiadiazol-2-ylamines **44**. The third modification was accomplished by treatment of resin **40** with Fmoc-protected isothiocyanates with DIPEA in DCM to yield hydrazine-1,2-dicarbothioamide resin **45**. Intermediate **45** was cyclized by treatment with EDC·HCl in NMP at 50 °C. Removal of the Fmoc-protecting group was followed by acylation with carboxylic acids using DIC in DCM/NMP. Cleavage with TFA and DCM yielded *N*-(5-alkylamino-1,3,4-thiadiazol-2-yl)-amides **46**.

After successful application of the synthesis protocol to the 1,3,4-thiadiazoles, the research group decided to apply it to the synthesis of the 1,3,4-oxadiazoles as well. Benzylamine resin **38** was treated with triphosgene and DIPEA in DCM, followed by reaction of the formed reactive intermediate with hydrazine hydrate in DMSO, to yield semicarbazide intermediate **47**. Thiobisurea resin **48** was then prepared by the reaction of intermediate **47** with various thiocyanates. The cyclization to the resin-bound 1,3,4-oxadiazoles **49** was performed with EDC·HCl in NMP at 50 °C. Subsequent cleavage from the polymer support with TFA and DCM yielded *N,N*-dialkyl-1,3,4-oxadiazole-2,5-diamines **50**. The resultant products of these studies showed good yield and purity.

Hwang et al.[75] developed reagent-based selective cyclization of the acyldithiocarbazate resins to the 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. The 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were synthesized using the dithiocarbazate linker. The Merrifield resin was used as a polymer support (Scheme 10). Merrifield resin **7** was treated with CS_2 and hydrazides in the presence of NaH to afford acyldithiocarbazate resin **51**. The cyclization of resin **51** was investigated with various agents, such as EDC·HCl, *N,N*′-dicyclohexylcarbodiimide (DCC), trimethylsilyl chloride (TMSCl), *p*-TsCl, PPh_3, $SOCl_2$, PCl_5, and diphenyl chlorophosphate. It was discovered that treatment with *p*-TsCl gives the 1,3,4-oxadiazole as a main product with high chemoselectivity (98%) and high overall yield (50%), whereas treatment with the TMSCl and diphenyl chlorophosphate selectively yield the 1,3,4-thiadiazole as a cyclized product (>98% selectivity, >50% overall yield). The desulfurative

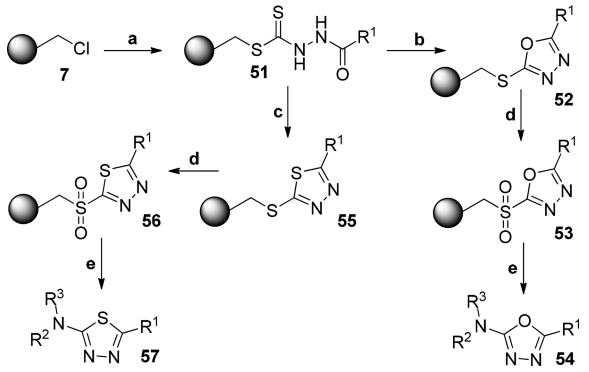
DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 9. Solid-Phase Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles[a]



[a]Reaction conditions: (a) (i) R^1NH_2, 5% AcOH, NMP/MeOH, 1 h; (ii) $NaBH_3CN$, NMP/MeOH, 12 h; (b) DPT, NMP, 50 °C, 16 h; (c) $NH_2NH_2{\cdot}xH_2O$, DMSO, 50 °C 14 h; (d) DPT, DCM, 3 h; (e) (i) 1,4-dioxane/MeOH/1 N NaOH (aq), 30 min; (ii) R^2Br, 1,4-dioxane, 14 h; (iii) TFA/DCM, 2 h; (vi) R^2CHO, TMOF/NMP, 16 h; (f) (i) $FeCl_3$, DCM/MeOH, 16 h; (ii) TFA/DCM, 2 h; (g) FmocNCS, DCM, DIPEA, 14 h; (h) (i) EDC·HCl, NMP, 50 °C, 14 h; (ii) DMF/piperidine; (iii) R^2COOH, DIIC, DMAP, DIPEA, NMP/DCM; (j) TFA/DCM, 2 h; (k) (i) $CO(OCCl_3)_2$, DIPEA, DCM, 5 h; (ii) $NH_2NH_2{\cdot}xH_2O$, DMSO, 14 h; (l) R^2NCS, DCM, DIPEA, 6 h; (m) (i) EDC·HCl, dry NMP, 50 °C, 14 h, (ii) TFA/DCM, 2 h.

Scheme 10. Solid-Phase Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles via Dithiocarbazate Linker[a]



[a]Reaction conditions: (a) hydrazides, CS_2, NaH, NMP, 12 h; (b) *p*-TsCl, Et_3N, DCE, 60 °C, 24 h; (c) TMSCl, DCE, 60 °C, 12 h; (d) *m*CPBA, 1 N (aq) NaOH, 1,4-dioxane, 6 h; (e) R^2R^3NH, 1,4-dioxane, 100 °C, 24 h.

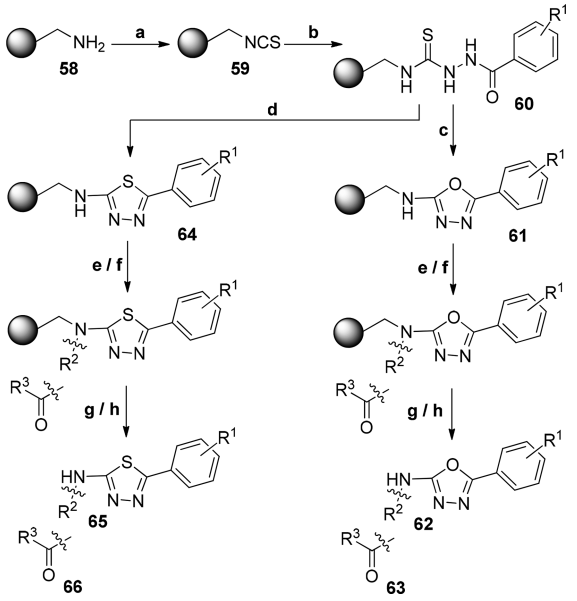
cyclization of acyldithiocarbazate resin **51** to the 1,3,4-oxadiazoles **52** was accomplished by the treatment of resin **51** with *p*-TsCl in 1,2-dichloroethane (DCE) at 60 °C for 24 h, whereas the reaction with TMSCl in DCE at 60 °C for 12 h resulted in dehydrative cyclization of acyldithiocarbazate resin **51** to 1,3,4-thiadiazoles **55**. The cleavage from the resin was performed by oxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA) with NaOH on 1,4-dioxane, and the formed sulfones **53** and **56** were treated with different amines in 1,4-dioxane at 100 °C, affording the desired 1,3,4-oxadiazoles **54** and 1,3,4-thiadiazoles **57**. The products were obtained in good yield (30−72%, 4-step overall yield) and high purity (>86%).

The reported synthetic methodology was upgraded by Yang et al. by replacing the dithiocarbazate linker by the backbone amide linker (BAL)[76] and improving the diversity of the synthesized compounds.[77] The synthetic methodology was first reported in solution phase with the replacement of the acyldithiocarbazate intermediate by the thiosemicarbazide intermediate.[78] Later, the solution-phase synthesis was successfully transferred to solid phase. In the new solid-phase synthetic approach, the 4-benzyloxy-2-methoxybenzylamine[79] (BOMBA) resin **58** was treated with CS_2, *p*-TsCl, and Et_3N in tetrahydrofuran (THF) to give the isothiocyanate-terminated resin **59** that was treated with benzhydrazides to obtain the thiosemicarbazide intermediate resin **60** (Scheme 11). The cyclization conditions were previously optimized in solution phase.[78] Accordingly, the cyclization of thiosemicarbazide intermediate **60** was performed using EDC·HCl and *p*-TsCl to give resin-bound 2-amino-1,3,4-oxadiazoles **61** and 2-amino-1,3,4-thiadiazoles **64**, respectively. Both 2-amino-1,3,4-oxadiazoles **61** and 2-amino-1,3,4-thiadiazoles **64** were then functionalized with various electrophiles, such as alkyl halides and acid chlorides, to generate resin-bound *N*-alkylamino, *N*-acylamino-1,3,4-oxadiazoles, and 1,3,4-thiadiazoles. The cleavage using TFA in DCM generated the desired *N*-alkylamino and *N*-acylamino-1,3,4-oxadiazoles (**62**, **63**) and 1,3,4-thiadiazoles (**65**, **66**) in moderate yield (5−63%, 5-step overall yield) and high purity (>89%).

Next, modification of the thiosemicarbazide intermediate was presented to boost the diversity of the 1,3,4-thiadiazole library (Scheme 12).[80] BOMBA resin **58** was converted to the isothiocyanate-terminated resin **59**; however, in this work, resin **59** was treated with hydrazine hydrate in DMSO to obtain hydrazine carbothioamide resin **67**. Resin **67** was reacted with acyl isothiocyanates in THF to afford the thiosemicarbazide intermediate **68**, which then underwent subsequent cyclization

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 11. Regioselective Solid-Phase Synthesis of 2-Amino-1,3,4-oxadiazoles and 2-Amino-1,3,4-thiadiazoles via BOMBA Resin[a]



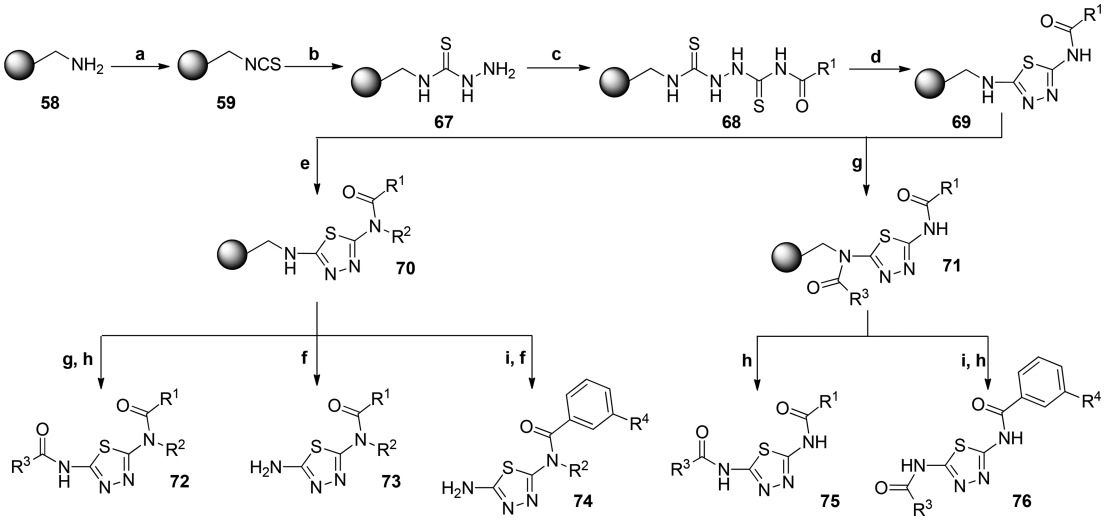
[a]Reaction conditions: (a) CS_2, *p*-TsCl, Et_3N, THF, 18 h; (b) benzhydrazide, Et_3N, THF, 16 h; (c) EDC·HCl, DMSO, 60 °C, 16 h; (d) *p*-TsCl, Et_3N, NMP, 12 h; (e) alkyl halide, *t*-BuOK, DMF, 60 °C, 16 h; (f) acid chloride, pyridine, 60 °C, 12 h; (g) TFA/DCM (1:4), 40 °C, 8 h; (h) TFA/DCM (1:4), 6 h.

in the presence of *p*-TsCl and pyridine in DCM. The resulting 2-amido-5-amino-1,3,4-thiadiazole resin **69** was functionalized through alkylation and acylation of the amide and acyl positions, as well as functionalization of the R1 position with Suzuki coupling. The cleavage from the resin was performed using TFA in a DCM cleavage cocktail. Synthesized compounds **72**−**76** were obtained in good yields and high purities.

In continuation of previous works, Ha et al. constructed the 1,3,4-oxadiazole and 1,3,4-thiadiazole library with a high level of skeletal diversity based on the branching diversity-oriented synthesis on solid phase.[81] Figure 4 shows a schematic of the library, which reveals the skeletal diversity was accomplished by functionalization of the 1,3,4-oxadiazole and 1,3,4-thiadiazole core skeletons with aryl, amide, urea, thiourea, amine, and peptide functional groups. Previously reported synthetic protocols were used for the cyclization of intermediate **60** to the 1,3,4-oxadiazole and 1,3,4-thiadiazole intermediates **61** and **64**.[77] Traditional synthetic methodologies were adapted for the diversification of the library. In total, Ha et al. synthesized 128 compounds **77**−**86** with 12 kinds of distinct library sets having aryl, urea, thiourea, amine, amide, and peptide chains on solid phase with high yields and purities.

In addition, we developed a solid-phase synthetic methodology for the synthesis of the 1,3,4-oxadiazole-based peptidomimetic library (Scheme 13).[82] The synthetic approach was based on the desulfurative cyclization of the intermediate thiosemicarbazide resin **87** that was obtained via coupling of the hydrazine carbothioamide resin **67** with Fmoc-protected amino acids in the presence of EDC·HCl and hydroxybenzotriazole-1-ol (HOBt) in DMF. Cyclization of intermediate **87** was conducted by treatment with *p*-TsCl and pyridine in THF at 60 °C, resulting in the 1,3,4-oxadiazole resin **88**. Next, acylation with 3-nitrobenzoyl chloride was performed using pyridine (neat) conditions to give resin **89**. The acylation with the 3-nitrobenzoyl functional group with following nitro-reduction can accommodate amide chain elongation from both sides of the core. By consecutive treatment of resin **89** with deprotection and amino acid coupling, resin-bound 1,3,4-oxadiazole **90** with peptide chain was obtained. Further reduction of the nitro functional group with tin(II) chloride in DMF gave resin **91**. Successive amino acid coupling and deprotection treatment with final cleavage from the resin afforded the desired library of 1,3,4-oxadiazole-based peptidomimetics with tripeptide chains on the two sides of the 1,3,4-oxadiazole core. The final compounds **92** were obtained in

Scheme 12. Solid-Phase Synthesis of 1,3,4-Thiadiazole Derivatives[a]



[a]Reaction conditions: (a) CS_2, *p*-TsCl, Et_3N, THF, 18 h; (b) $NH_2NH_2{\cdot}xH_2O$, DMSO, 50 °C, 4 h; (c) acyl isothiocyanate, THF, 3 h; (d) *p*-TsCl, pyridine, DCM, 5 h; (e) alkyl halide, NaH, DMF, 60 °C, 16 h; (f) TFA/DCM (1:4, v/v), 40 °C, 4 h; (g) acid chloride, pyridine, 16 h; (h) TFA/DCM (1:4, v/v), 4 h; (i) boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O (9:1), 80 °C, 20 h.

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

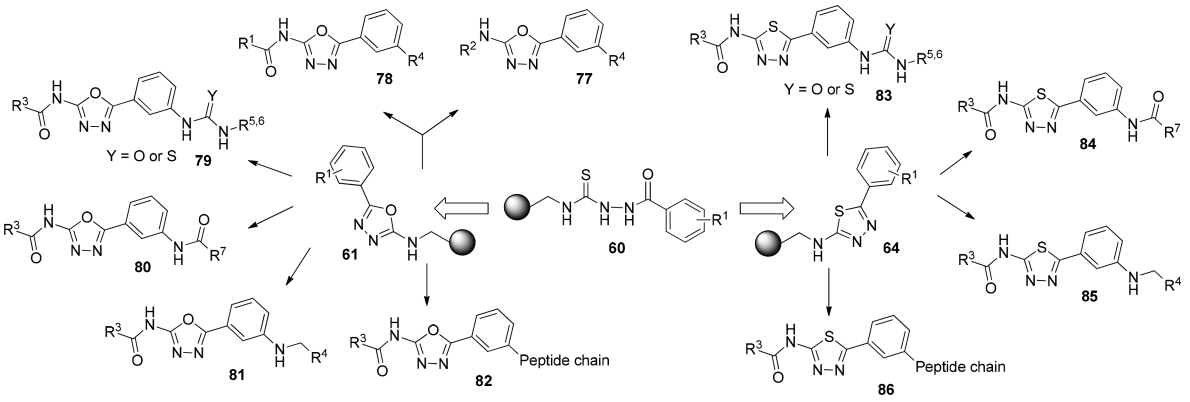
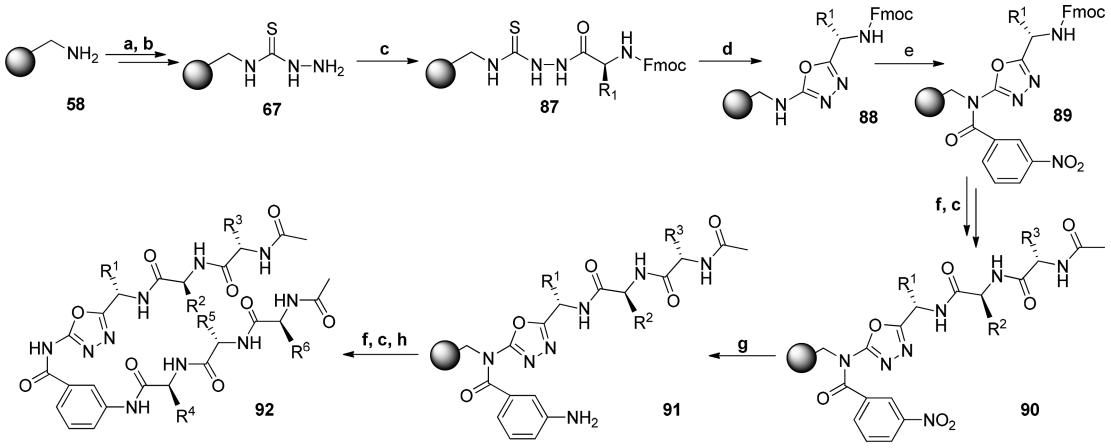


Figure 4. 1,3,4-Oxadiazole and 1,3,4-thiadiazole library with a high level of skeletal diversity.

Scheme 13. Solid-Phase Synthesis of the 1,3,4-Oxadiazole-Based Peptidomimetic Library[a]

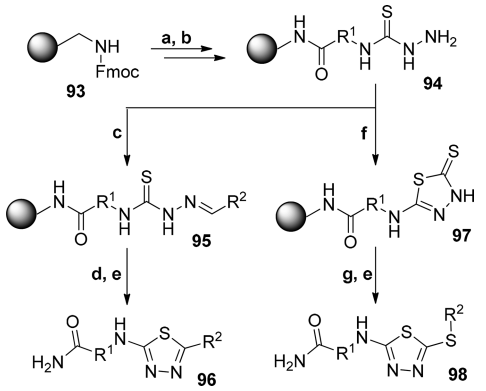


[a]Reaction conditions: (a) CS_2, *p*-TsCl, TEA, THF, 18 h; (b) $NH_2NH_2{\cdot}xH_2O$, DMSO, 50 °C, 4 h; (c) Fmoc-protected amino acid or AcOH, EDC·HCl, HOBt, 24 h; (d) *p*-TsCl, pyridine, THF, 60 °C, 16 h; (e) 3-nitrobenzoyl chloride, pyridine, 60 °C, 16 h; (f) 20% piperidine, DMF, 1 h; (g) $SnCl_2{\cdot}2H_2O$, DMF, 16 h; (h) TFA, DCM, 4−6 h.

moderate-to-good yields ((5−27) %, 20-step overall yield) and high purities (>90%). In addition, the chain length can be regulated with this methodology, and compounds with shorter or longer chains can easily be prepared.

There are not many reports on the solid-phase synthesis of the 1,3,4-thiadiazoles. Aside from the already discussed articles that include the synthesis of the 1,3,4-thiadiazoles, there are a few additional records that we will discuss next. Kilburn et al. presented one of the earliest reports on the solid-phase synthesis of the 1,3,4-thiadiazoles.[83] Rink amide resin was used for the synthesis of the compounds, and two synthetic routes were introduced (Scheme 14). First, Fmoc-protected amino acid was attached to the Rink amide resin **93** with subsequent conversion to the isothiocyanate resin using di(2-pyridyl)-thionocarbonate (DPT) and then to the thiosemicarbazide resin **94** using hydrazine hydrate. The R1 represented in Scheme 14 was held constant as 1,4-phenylene-CH_2-(N). In the first approach, thiosemicarbazide resin **94** was converted to the thiosemicarbazone intermediate **95** with adding aldehydes in an acidic medium of DMF and TMOF. For the cyclodehydration, the research group used iron(III) chloride in DCM and MeOH. The cyclized resin was then released from the solid support with TFA in DCM to give the desired 1,3,4-thiadiazole derivatives **96**. In the second approach, intermediate **94** was treated with DPT in DCM to give resin-bound thione **97**. The monoalkylation of thione resin **97** was performed next with α-haloketones in basic conditions. The cleavage from the resin was also conducted with TFA in DCM to give 2-alkylthio-

Scheme 14. Solid-Phase Synthesis of 1,3,4-Thiadiazole Derivatives by Kilburn et al.[a]



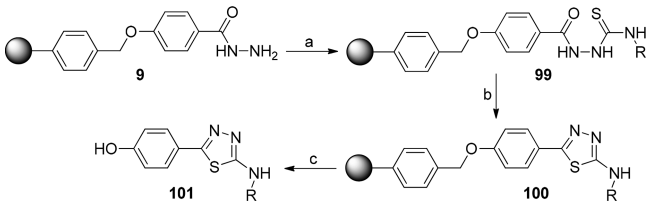
[a]Reaction conditions: (a) (i) deprotection, $HOOCR^1NHFmoc$, PyBrOP, DIPEA, NMP, 4 h; (ii) deprotection, DPT, DCM, 2 h; (b) $NH_2NH_2{\cdot}xH_2O$, NMP, 5 h; (c) R^2CHO, DMF:TMOF:AcOH (9:9:2), 5 h; (d) $FeCl_3{\cdot}6H_2O$, DCM:MeOH (2:1), 20 h; (e) TFA:DCM (2:1), 1 h. (f) DPT, DCM, 4 h; (g) R^2X, 1,4-dioxane, 16 h.

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

1,3,4-thiadiazole derivatives **98**. The products were obtained in good yields and excellent purities.

Liu et al. previously reported the synthesis of the 1,3,4-oxadiazoline-5-thione derivatives from acylhydrazines.[69] In continuation of this work, they reported the solid-phase synthesis of the 1,3,4-thiadiazoles using the same intermediate acylhydrazine resin **9** (Scheme 15).[84] The acylhydrazine resin **9**

Scheme 15. Solid-Phase Synthesis of 2-Arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole Derivatives[a]

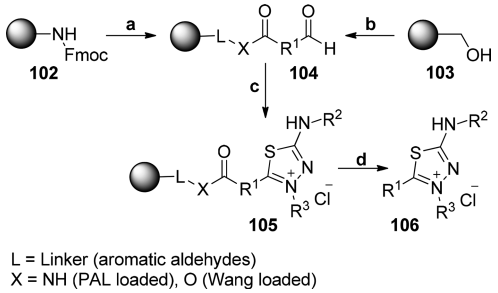


[a]Reaction conditions: (a) RNCS, EtOH, reflux, 6 h; (b) concd H_2SO_4, 4 h; (c) TFA, DCM.

was reacted with excess of the isothiocyanates in EtOH to afford thiosemicarbazide resin **99**. The cyclization of resin **99** was accomplished with concentrated H_2SO_4, resulting in 1,3,4-thiadiazole resin **100**. The desired 2-arylamino-5-(4-hydroxyphenyl)-1,3,4-thiadiazole derivatives **101** were obtained by cleavage from the resin with TFA in DCM with good yields and purities.

Kappel et al. developed the solid-phase syntheses of 1,3,4-thiadiazolium-2-aminides from resin-bound aromatic aldehydes (Scheme 16).[85] For the synthesis, they used polyethylene

Scheme 16. Solid-Phase Synthesis of 1,3,4-Thiadiazolium-2-aminides from Resin-Bound Aromatic Aldehydes[a]

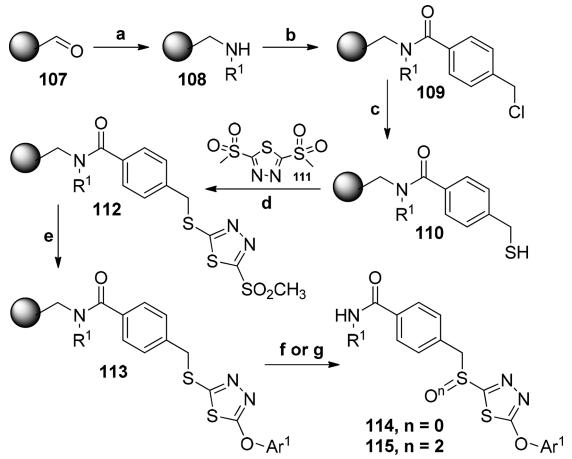


[a]Reaction conditions: (a) (i) piperidine:DMF (1:4); (ii) aromatic aldehyde, HATU, DIPEA, DMF, 1 h; (b) aromatic aldehyde, DIC, DMAP, DMF, 1 h; (c) 1,4-disubstituted thiosemicarbazide, TMSCl, 1,4-dioxane:THF (2:1), 60 °C, 2 h; (d) TFA:H_2O (19:1), 2 h.

glycol-polystyrene resin **102** (Fmoc-PAL-PEG-PS or PAL-PEG-PS) and Wang resin **103**. First, various aromatic aldehydes were attached to resins **102** and **103** in the presence of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxide hexafluorophosphate (HATU) with DIPEA in DMF and DIC with 4-dimethylaminopyridine (DMAP), respectively, resulting in aldehyde resins **104**. Resin **104** was reacted with a number of 1,4-disubstituted thiosemicarbazides (prepared separately in solution phase). The cyclization reaction was accomplished with TMSCl in 1,4-dioxane and THF to yield resin-bound cyclic intermediates **105**. Finally, cleavage from the resin was conducted with TFA/H_2O to give 1,3,4-thiadiazolium-2-aminides **106** in good yields and high purities.

Pernerstorfer et al. reported the solid-phase synthesis of the focused 1,3,4-thiadiazole ether library.[86] In the presented methodology, they used 2,5-bis(methylsulfonyl)-1,3,4-thiadiazole **111** as a key intermediate (Scheme 17). The library

Scheme 17. Solid-Phase Synthesis of the Focused 1,3,4-Thiadiazole Ether Library[a]



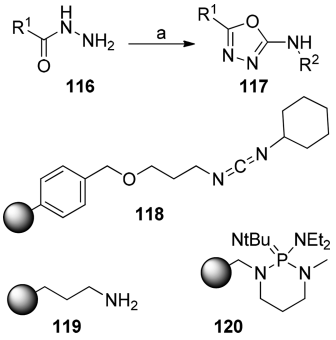
[a]Reaction conditions: (a) (i) R^1NH_2, TMOF, toluene, 65 °C, overnight; (ii) Bu_4NBH_4, AcOH, DMF, −40 °C, 20 min; (b) 4-chloromethylbenzoyl chloride, DIPEA, DCM, 2 h; (c) (i) $SC(NH_2)_2$, 1,4-dioxane, 65 °C, overnight; (ii) $C_2H_4N_2H_4$, 1,4-dioxane:H_2O (10:1), 65 °C, 3 h; (d) **111**, DMAP, DMF, 2 h; (e) Ar^1OH, Cs_2CO_3, DMA, 6 h; (f) TFA, 15 min × 4; (g) (i) *m*CPBA, 1,4-dioxane:2-propanol (3:1), 5 h; (ii) TFA, 15 min × 4.

synthesis starts from *n*-propylamine and 4-fluoroaniline reductively alkylated with aldehyde 4-(4-formyl-3-methoxyphenoxy)butyryl aminomethyl resin **107**, by imine formation and subsequent reduction of the imines with tetrabutylammonium borohydride (Bu_4NBH_4), to afford resin **108**. Further acylation with 4-chloromethylbenzoyl chloride in the presence of DIPEA and DCM resulted in the benzyl halide resin **109**, which was converted to thiol resin **110**. The introduction of intermediate **111** to thiol resin **110** was conducted in the presence of DMAP in DMF, affording resin **112** with 1,3,4-thiadiazole. The sulfone group in 1,3,4-thiadiazole resin **112** was smoothly replaced with a set of phenols using Cs_2CO_3 in dimethylacetamide (DMA) to obtain 1,3,4-thiadiazolyl ether resin **113**. The cleavage from the resin was performed in two ways: (a) via TFA to afford 1,3,4-thiadiazolyl ethers **114** and (b) via preliminary oxidation with *m*CPBA and further cleavage with TFA to afford 1,3,4-thiadiazolyl sulfones **115**.

1.3. Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles Using Resin-Bound Reagents. The resin-bound reagents are commercially available and can be used for rapid parallel synthesis because of the easy and safe reagent handling and simple product isolation. Coppo et al. reported the one-pot solution-phase synthesis of 2-amino-1,3,4-oxadiazoles using resin-bound reagents (Scheme 18).[87] The one-pot synthesis started from the preparation of acyl hydrazines **116** by addition of the isothiocyanates to a solution of the hydrazide in DMF. The resulting solution was stirred overnight (20 h); PS-carbodiimide **118** was added directly to the reaction mixture with an additional DMF to accommodate swelling of the resin,

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 18. One-Pot Synthesis of 5-Substituted 2-Amino-1,3,4-oxadiazoles Using Resin-Bound Reagents[a]

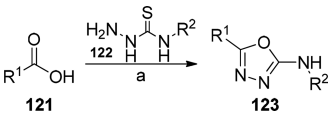


[a]Reaction conditions: (a) (i) R^2NCS, DMF, 20 h; (ii) **118**, DMF, 80 °C, 60 h; (iii) **119**, **120**, 17 h.

and the reaction mixture was shaken at 80 °C for 60 h. Next, P-propylamine **119** and PS-BEMP **120** were added, and the resin suspension was shaken for an additional 17 h. The filtrate was collected after simple filtration and washing with THF, and evaporation of the filtrate resulted in the desired 2-amino-1,3,4-oxadiazole derivatives **117**. The products were obtained in excellent purities and good yields.

Chekler et al. reported the one-pot synthesis of substituted 2-amino-1,3,4-oxadiazoles using resin-bound EDC (Scheme 19).[88] Initially, the research team prepared 2-amino-1,3,4-

Scheme 19. One-Pot Synthesis of Substituted 2-Amino-1,3,4-oxadiazoles via Resin-Bound EDC[a]

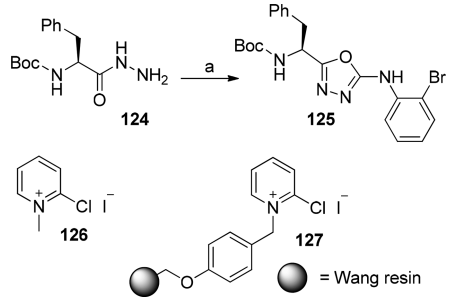


[a]Reaction conditions: (a) **122**, resin-bound EDC, DMF.

oxadiazole derivatives using only soluble reagents; however, to improve the reaction conditions and explore the scope and limitations of the reaction conditions, they replaced EDC by the resin-bound EDC. Scheme 19 shows that carboxylic acid **121** reacted with thiosemicarbazide **122** in the presence of polymer-bound EDC in DMF. The corresponding 1,3,4-oxadiazole **123** remains in solution, and the resin can be easily removed upon completion of the reaction.

Gavrilyuk et al. presented another example of this technique (Scheme 20).[89] Their work was dedicated to the synthesis of amino acid-derived 2-arylamino-1,3,4-oxadiazoles. Accordingly, they reported the solution-phase synthesis of 5-substituted 2-arylamino-1,3,4-oxadiazoles from the amino acid-derived acylthiosemocarbazides via $HgCl_2$ and Et_3N in MeCN. However, because the authors wanted to avoid the use of $HgCl_2$, they found an alternative dehydrothiolating agent, Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide, CMPI) **126** and its polymer equivalent **127**. They compared the formation of 1,3,4-oxadiazole **125** from the acylthiosemocarbazide **124** using these three reagents with the following results: all three reactions were completed with excellent yields (92% for $HgCl_2$, 94% for CMPI, and 95% for resin-bound CMPI) and high purities (>98%). The use of the resin-bound CMPI **127** avoids the toxicity and environmental problems associated with the use of mercury salts and requires only

Scheme 20. Synthesis of Amino Acid-Derived 2-Arylamino-1,3,4-oxadiazoles via Resin-Bound Mukaiyama's Reagent[a]

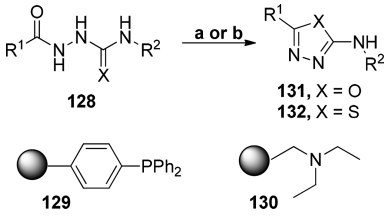


[a]Reaction conditions: (a) (i) 2-BrC_6H_4NCS, DCM, 20 min; (ii) **127**, Et_3N, MeCN:DCM (1:1), 16 h.

simple filtration upon completion of the reaction. The crude sample showed excellent purity, and column chromatographic purification was not required.

Baxendale et al. used polymer-supported reagents and microwave heating to synthesize 2-aminosulfonamide-1,3,4-oxadiazoles and their 1,3,4-thiadiazole analogues.[90] The cyclodehydration of (thio)semicarbazide intermediates **128** with a resin-bound DCC **118** in DMF at 140 °C for 1 h under microwave irradiation (MW) was excellent (Scheme 21, route

Scheme 21. Synthesis of 2-Aminosulfonamide-1,3,4-oxadiazoles and 1,3,4-Thiadiazoles[a]



[a]Reaction conditions: (a) **118**, DMF, MW 140 °C, 1 h; (b) **129**, **130**, CBr_4, 3 h.

a), leading cleanly to the desired 1,3,4-oxadiazoles **131** and 1,3,4-thiadiazoles **132** in good yields (64−88%). However, 6 equiv of the resin-bound DCC **118** was required for the reaction completion; thus, alternative approaches were needed. The authors found an alternative in the mixture of a resin-bound PS-triphenylphosphine **129** and carbon tetrabromide with an immobilized Et_3N **130** (Scheme 21, route **b**). The reporting conditions gave high conversion, although the purities of the obtained products were lower than those for the compounds obtained in the previous PS-DCC-mediated method (78−92%). However, the problem was solved with simple filtration of the reaction mixture through a functionalized silica-packed cartridge (aminopropyl-NH_2) that significantly improved the purities (>95%). Additionally, they studied the effect of the base and compared various polymer-supported bases as well as the effect of the solvent.

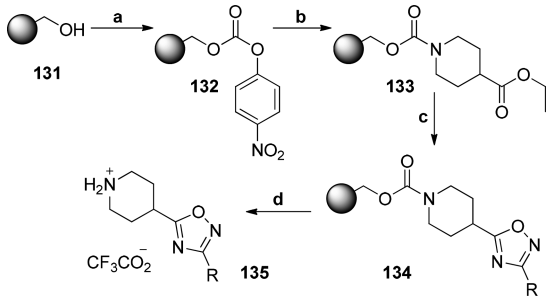
2. Solid-Phase Synthesis of 1,2,4-Oxadiazoles. The 1,2,4-oxadiazoles can generally be prepared from (a) the amidoximes reacting with acid derivatives (esters, acid chlorides, and anhydrides with further cyclization of the obtained intermediate) and amides, (b) a ring closure of monoximes and diacylamides, (c) a reaction of nitrile oxides

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

with nitriles, or (d) ring transformations from other aromatic rings.[4c]

The solid-phase synthesis of 1,2,4-oxadiazoles was mainly accomplished from amidoximes and nitriles. Liang et al. presented one of the first reports on the solid-phase synthesis of 1,2,4-oxadiazoles (Scheme 22).[91] TentaGel resin **131** was reacted with *p*-nitrophenyl chloroformate with subsequent treatment with ethyl isonipecotate to give resin **133**. Both reactions were conducted in the presence of DIPEA and DCM. Next, the resin-bound ethyl isonipecotate was reacted with various amidoximes and NaOEt in EtOH for 3 days at rt to yield cyclized product **134**. Resin **134** was cleaved using TFA in DCM, and the desired 1,2,4-oxadiazole derivatives **135** were obtained as its TFA salt form with high yields (>75%) and purities (>90%).

Scheme 22. Solid-Phase Synthesis of 1,2,4-Oxadiazoles via TentaGel Resin[a]

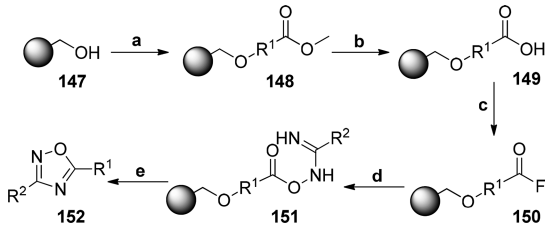


[a]Reaction conditions: (a) *p*-nitrophenyl chloroformate, DIPEA, DCM; (b) ethyl isonipecotate, DIPEA, DCM; (c) amidoximes, NaOEt, EtOH, 3 days; (d) TFA, DCM, 30 min.

Hebert et al. reported the solid-phase synthesis of the 1,2,4-oxadiazoles using resin-bound nitriles **136** modified from the MBHA resin and *p*-alkoxybenzyl bromide resin.[92] Resin-bound nitriles **136** were reacted with hydroxylamine hydrochloride and DIPEA in 2-methoxyethanol at 85 °C for 16 h, affording the amide oximes **137** in quantitative yield (Scheme 23). Amide oxime resin **137** was treated with Fmoc and Boc-protected amino acid anhydrides with further cyclization using 2-methoxyethyl ether to give 1,2,4-oxadiazole resin **139**. After removing the protecting groups (PG) with an appropriate protocol, the resulting amines **140** were functionalized with acylating and sulfonylating agents to give amides **141** and sulfonamides **142**, respectively. Another synthetic route was proposed by converting amide oxime resin **137** to the 5-chloromethyl 1,2,4-oxadiazole resin **143** via chloroacetic anhydride in 2-methoxyethyl ether. The amination of resin **143** with the primary amines resulted in the 5-aminomethyl-1,2,4-oxadiazole resin **144**. Resin **144** was also treated with a number of acylating and sulfonylating agents to give amides **145** and sulfonamides **146**, respectively.

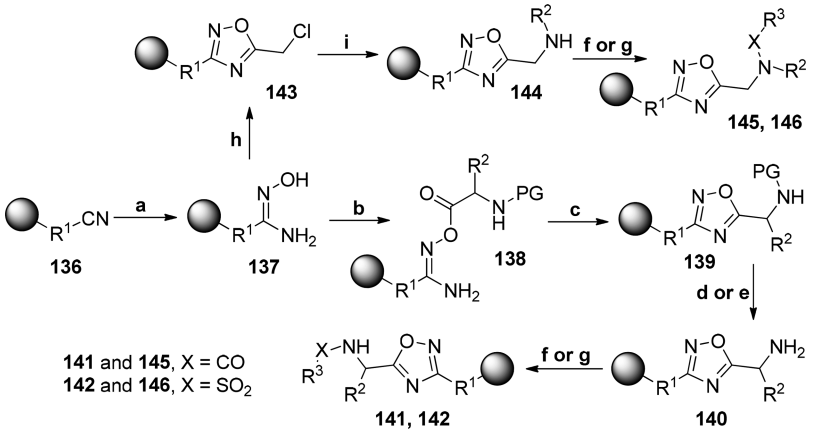
Sams et al. developed the solid-phase synthesis of the 1,2,4-oxadiazoles from solid-supported benzoic acids (Scheme 24).[93] The solid-phase synthesis starts from attaching benzoic acid methyl esters to Wang resin **147** via phenolic linkage with subsequent hydrolysis of the esters **148** to the resin-bound carboxylic acids **149**. The conversion of the carboxylic acid to the acid fluoride **150** was performed via treatment with cyanuric fluoride. Next, the acyl fluoride was reacted with *N*-hydroxylamidines that were prepared separately in solution phase from nitriles and hydroxylamine. Subsequent heating of

Scheme 24. Solid-Phase Synthesis of 1,2,4-Oxadiazoles from Resin-Bound Benzoic Acids[a]



[a]Reaction conditions: (a) (i) CH_3SO_2Cl, DIPEA, DCM; (ii) $HOR^1CO_2CH_3$, Cs_2CO_3, NMP; (b) $KOSiMe_3$, THF, AcOH; (c) cyanuric fluoride, DCM/NMM (2:1), 2 h; (d) *N*-hydroxylamidines, NMP/NMM (3:1), 24 h; (e) (i) NMP, 125 °C, 16 h; (ii) 50% TFA in DCM.

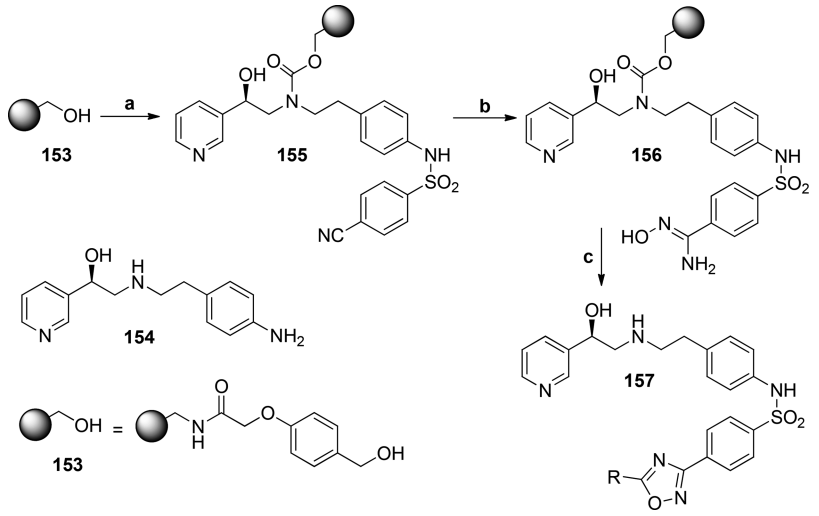
Scheme 23. Solid-Phase Synthesis of 1,2,4-Oxadiazoles from Nitriles[a]



[a]Reaction conditions: (a) $NH_2OH{\cdot}HCl$, DIPEA, $CH_3OCH_2CH_2OH$, 85 °C, 16 h; (b) Boc-NHR^2-CO_2H or Fmoc-NHR^2-CO_2H, DIC, 2-methoxyethyl ether, 1 h, then 60 °C, 16 h; (c) 2-methoxyethyl ether, 85 °C, 6 h; (d) 50% TFA, DCM; (e) 20% piperidine, DMF; (f) R^3CO_2H, DIC/DMAP or PyBOP, DIPEA, DCM/DMF (2:1); (g) R^3SO_2Cl, NMM, NMI, CH_3CN or THF; (h) $(ClCH_2CO)_2O$, 2-methoxyethyl ether, 60 °C, 16 h, then 85 °C, 6 h; (i) R^2NH_2, DMF.

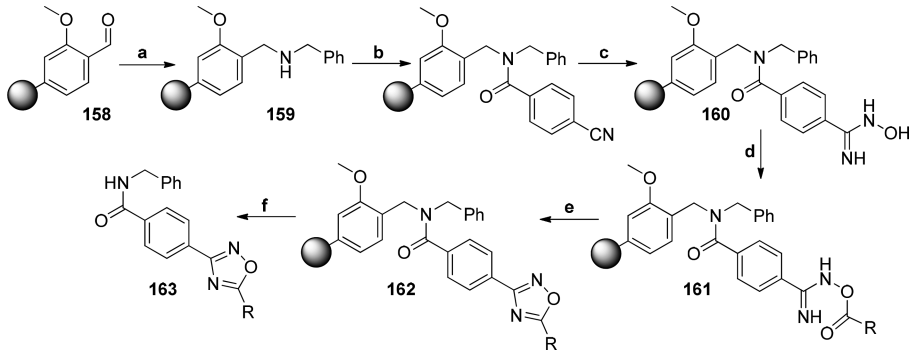
DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 25. Solid-Phase Synthesis of 1,2,4-Oxadiazoles Benzenesulfonamides[a]



[a]Reaction conditions: (a) (i) **154**, 4-nitrobenzoyl chloride, $(C_2H_5)_3SiCl$, base; (ii) 4-cyanobenzenesulfonyl chloride, pyridine, DCM; (b) $NH_2OH\cdot HCl$, K_2CO_3, EtOH, reflux; (c) (i) RC(O)X, (X = OH, Cl, −OCOR), 110 °C, 2−15 h; (ii) TFA in DCM.

Scheme 26. Solid-Phase Synthesis of 1,2,4-Oxadiazoles from *O*-Acyl Amidoximes[a]



[a]Reaction conditions: (a) $(MeO)_3CH$, $PhCH_2NH_2$; $NaBH_3CN$, AcOH, THF; (b) 4-cyanobenzoyl chloride, DMAP, pyridine, DMF; (c) 50% (aq) NH_2OH, EtOH, reflux; (d) RCOCl, pyridine, DMF; (e) TBAF, THF; (f) 95% TFA.

the acylated *N*-hydroxyamidine **151** with subsequent cleavage using 50% TFA in DCM afforded the 1,2,4-oxadiazole derivatives **152** in moderate yields (24−40%) and good purities (>60%).

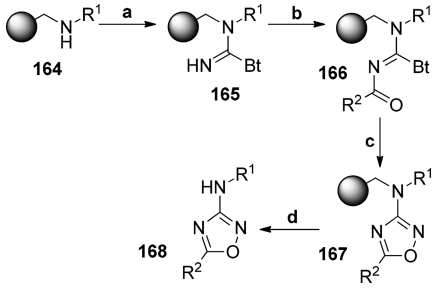
Biftu et al. reported the synthesis of benzyl and phenoxymethylene 1,2,4-oxadiazole benzenesulfonamides using hydroxymethyl phenoxyacetic acid (HMPA) resin **153** (Scheme 25).[94] Aniline derivative **154** was linked to resin **153** and treated with 4-cyanobenzenesulfonyl chloride and pyridine in anhydrous DCM at 0 °C to give sulfonamide resin **155**. Sulfonamide **155** was then reacted with hydroxylamine hydrochloride and K_2CO_3 in EtOH at reflux, resulting in the amidoxime resin **156**. The acylation of resin **156** with acid chlorides and anhydrides with subsequent heating at 110 °C in pyridine or diglyme for 2−15 h afforded 1,2,4-oxadiazole benzenesulfonamide resin. Cleavage from the resin using TFA in MC afforded the desired 1,2,4-oxadiazole benzenesulfonamide derivatives **157** in moderate yields (30−50%).

Rice et al. reported the solid-phase synthesis of 1,2,4-oxadiazoles via TBAF-mediated cyclodehydration of *O*-acyl amidoximes.[95] Agropore MB-CHO resin **158** was used as a solid support (Scheme 26). The synthesis process starts from the reductive amination of resin **158** with an excess of the benzylamine in trimethyl orthoformate followed by imine reduction with sodium cyanoborohydride to give resin **159**. The acylation of the benzylamine resin **159** with 4-cyanobenzoyl chloride was performed using pyridine and a catalytic amount of DMAP in DMF. The resulting nitrile resin was converted to amidoxime **160** by treatment with an excess of hydroxylamine in EtOH at reflux for 1 h. Amidoxime resin **160** underwent acylation with various acid chlorides in the presence of pyridine in DMF for 30 min. The formed acylated resin **161** was then treated with TBAF in THF for over 12 h to yield cyclized resin **162**. The cleavage from the resin was conducted by using 95% (aq) TFA to give the desired 1,2,4-oxadiazoles **163** in moderate yields (15−52%) and purities (>55%).

Makara et al. reported a solid-phase synthesis of 3-alkylamino-1,2,4-oxadiazoles from the *N*-acyl-1*H*-benzotriazole-1-carboximidamides.[96] Scheme 27 shows the synthesis strategy. The resin-bound secondary amine resin **164** was converted to the resin-bound benzotriazole carboximidamide **165** using di(benzotriazolyl)methanimine reagent and reacted with acyl chlorides in the presence of DIPEA in DCM to give the *N*-acyl-1*H*-benzotriazole-1-carboximidamide intermediate resin **166**. Resin **166** was subjected to cyclization with excess hydroxylamine hydrochloride with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in THF. Although THF was effective in

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 27. Solid-Phase Synthesis of 3-Alkylamino-1,2,4-oxadiazoles[a]



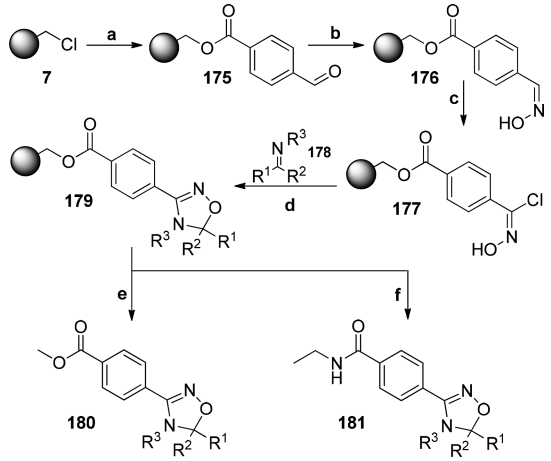
[a]Reaction conditions: (a) $Bt_1C(NH)Bt_1$:$Bt_1C(NH)Bt_2$, THF; (b) R_2COCl, DIPEA, DCM; (c) $NH_2OH{\cdot}HCl$, DBU, THF or DMA, 50 °C; (d) TFA/DCM (95:5).

the cyclocondensation step, DMA proved to be equally effective. Cyclized resin **167** was cleaved, and 3-alkylamino-1,2,4-oxadiazole derivatives **168** were obtained in high yields (>75%) and purities (>65%).

Quan et al. developed the solid-phase synthesis of 5-isoxazol-4-yl-[1,2,4]oxadiazoles via condensation of the benzamidoximes.[97] The synthetic approach was first conducted in solution phase and then transferred to solid phase (Scheme 28). First, Wang resin **147** was converted to the trichloroacetimide resin **169** by treatment with trichloroacetonitrile and DBU. Next, resin **169** was treated with 3-butyn-2-ol and a catalytic amount of $BF_3{\cdot}OEt_2$ to give resin-bound benzyl ether **170**. Treatment of resin **170** with lithium diisopropylamide (LDA) and subsequent *C*-acylation with methyl chloroformate was accomplished overnight at rt. The resulting resin **171** underwent 1,3-dipolar cycloaddition with benzaldehyde oximes in the presence of NaOCl in THF for 3 days. The obtained resin-bound isoxazole resin **172** containing carboxylic acid methyl ester was converted to the resin-bound isoxazole-substituted carboxylic acid resin **173** via saponification using LiOH in the mixture of water, MeOH, and THF. Cyclization of resin **173** to the 1,2,4-oxadiazole was performed by its condensation with benzamidoximes and further cleavage, affording desired products **174** in moderate yields (7−27%).

Lin et al. presented the one-pot solid-phase synthesis of 1,2,4-oxadiazoles by 1,3-dipolar cycloaddition of nitrile oxides with imines.[98] Scheme 29 shows the detailed synthesis process. The synthesis process starts from the attachment of the cesium salt of 4-formylbenzoic acid to Merrifield resin **7** with further conversion of the formed resin **175** to the aldoxime resin **176**.

Scheme 29. One-Pot Solid-Phase Synthesis of 1,2,4-Oxadiazoles[a]

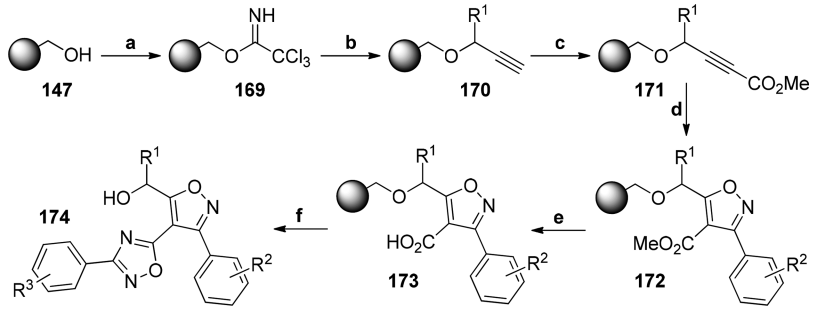


[a]Reaction conditions: (a) $CsCO_2C_6H_4CHO$, DMF; (b) $NH_2OH{\cdot}HCl$, Et_3N, MeOH/DCM, 48 h; (c) NCS, DCM, 6 h; (d) **178**, Et_3N, 36 h; (e) 0.5 M MeONa, MeOH/THF (1:4), 12 h; (f) 70% $EtNH_2$, H_2O/THF (1:1), 40 °C, overnight.

Subsequent reaction of the aldoxime resin **176** with an excess of the *N*-chlorosuccinimide (NCS) in DCM for 6 h afforded chlorooxime resin **177**. Next, various imines **178** (prepared separately in solution phase) were added to the reaction mixture of resin **177** with the subsequent addition of Et_3N. The resulting mixture was shaken for 36 h to provide 1,2,4-oxadiazole resin **179**. The cleavage from the solid support was performed in two ways: (a) by treatment with 0.5 M MeONa in MeOH/THF (1:4) at rt for 12 h to give compounds **180** and (b) by treatment with 70% of ethylamine in H_2O/THF (1:1) at 40 °C overnight to give ethyl amides **181**. The resulting library of 1,2,4-oxadiazole derivatives was obtained in high yields (64−96%) and purities (>80%).

In continuation of their studies, Lin et al. replaced Merrifield resin with the soluble polymer support polyethylene glycol (PEG).[99] The synthetic strategy was partly modified because of the new polymer support (Scheme 30). Preparation of aldehyde resin **183** was conducted by treatment of PEG resin **182** with 4-formyl benzoic acid in the presence of DCC and DMAP in anhydrous DCM for 24 h at rt. Next, resin **183** was converted to the aldoxime resin **184** with further chlorination to give chlorooxime resin **185**. Resin **185** was reacted with an excess of various imines in DCM with the slow addition of

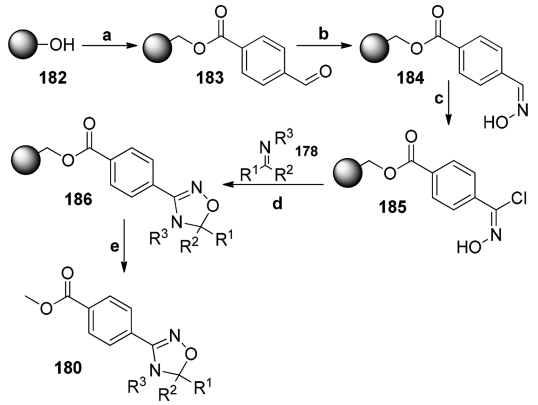
Scheme 28. Solid-Phase Synthesis of 5-Isoxazol-4-yl-[1,2,4]oxadiazoles[a]



[a]Reaction conditions: (a) Cl_3CCN, DBU, 0 °C, 1 h; (b) 3-butyn-2-ol, $BF_3.OEt_2$; (c) (i) LDA, −78 °C; (ii) $ClCO_2Me$; (d) benzaldehyde oximes, NaOCl, THF, H_2O, 3 days; (e) LiOH, H_2O, MeOH, THF, 3 days; (f) (i) benzamidoximes, EDC, DMF, 75 °C; (ii) TFA:DCM (1:1).

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 30. Solid-Phase Synthesis of 1,2,4-Oxadiazoles via PEG Resin[a]



[a]Reaction conditions: (a) $HCO_2C_6H_4CHO$, DCC, DMAP, DCM, 24 h; (b) $NH_2OH{\cdot}HCl$, TOA, DCM, 24 h; (c) NCS, DCM; (d) **178**, TOA, overnight; (e) 0.1 M MeONa, MeOH, 6 h.

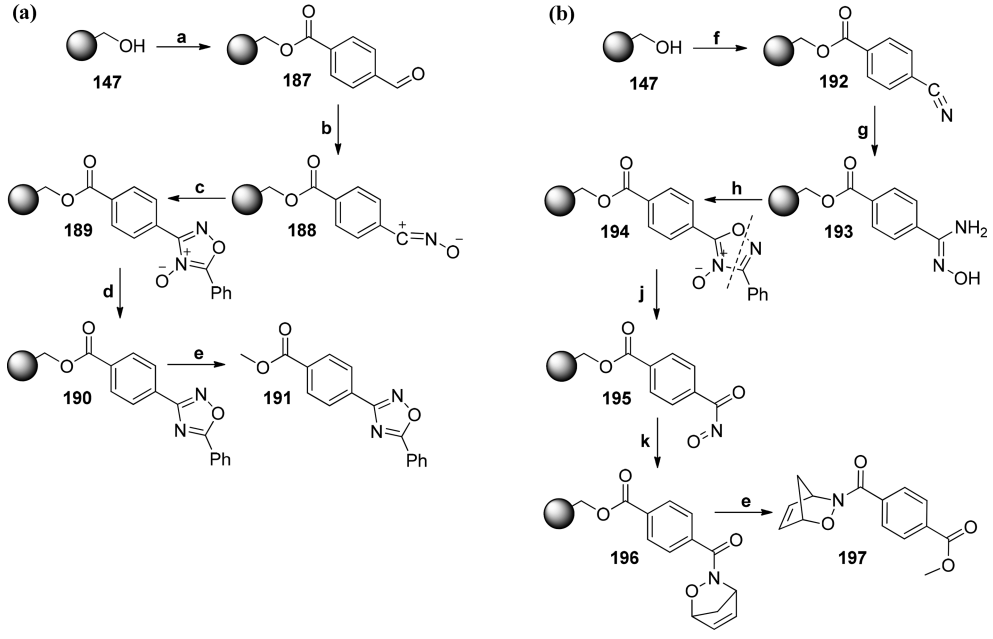
trioctylamine (TOA). After shaking the reaction mixture overnight at rt, the PEG-bound 4,5-dihydro-1,2,4-oxadiazoles **186** were obtained. Products **180** were released from the polymer support by treatment with MeONa in MeOH for 6 h at rt. The products were obtained in higher yields (79−93%) and purities (>89%) as compared to the previous report.

Quadrelli et al. developed solid-phase synthesis of the 3,5-substituted 1,2,4-oxadiazoles and studied their photochemical generation of the nitrosocarbonyl intermediates.[100] The synthesis of 1,2,4-oxadiazoles was performed in two ways, both using cycloaddition of nitrile oxides with amidoximes. In the first approach (Scheme 31a), they converted Wang resin **147** to the aldehyde resin **187** by reaction with 4-carboxybenzaldehyde and DIC/DMAP in DCM with subsequent conversion of resin **187** to the nitrile oxide resin **188**. Nitrile oxide resin **188** was then subjected to cycloaddition with benzamidoxime in toluene for 48 h to give resin-bound *N*-oxide **189**. The heating of resin-bound *N*-oxide **189** with an excess of $(EtO)_3P$ in benzene resulted in 1,2,4-oxadiazole resin **190**. Cleavage from the resin via the transesterification method afforded 3-(4-carbomethoxyphenyl)-5-phenyl-1,2,4-oxadiazole **191** in 17% yield. Furthermore, compound **191** was subjected to studies of the photochemical generation potential of nitrosocarbonyl intermediates and treated with light (sunlight, 310 nm) in MeOH to obtain various products.

In the second approach (Scheme 31b), the Wang resin was converted to nitrile resin **192** with subsequent transformation to amidoxime resin **193** using standard reaction conditions. Further addition of the nitrile oxides to amidoxime resin **193** afforded the reversed resin-bound 1,2,4-oxadiazole-4-oxide **194**. The presence of the reversed 1,2,4-oxadiazole-4-oxide was then detected through its photolysis and trapping of the resin-bound nitrosocarbonyl intermediate **195** with cyclopentadiene. Resin **194** was suspended in MeOH and treated with an excess of cyclopentadiene with subsequent irradiation to afford resin-bound cycloadduct **196**. Cleavage from the resin using the transesterification technique resulted in desired product **197** in 18% yield and Wang resin that could be used again.

Huang et al. developed solid-phase synthesis of linked heterocycles from a selenopolystyrene resin that included 1,2,4-oxadiazoles.[101] The selenopolystyrene resin was introduced earlier (Scheme 6) and was developed by the same research group. In this synthesis strategy (Scheme 32), polystyrene-bound selenium bromide **18** was reacted with acrylic acid in the presence of $ZnCl_2$ for 2 h with subsequent treatment by *t*-BuONa to give selenoacrylic acid resin **199**. With resin **199**, researchers developed two routes for the synthesis of the

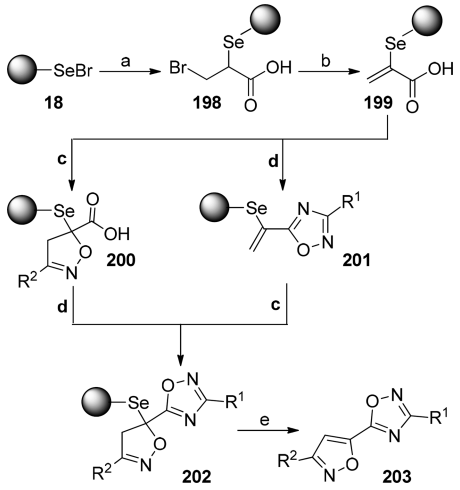
Scheme 31. Solid-Phase Synthesis of 1,2,4-Oxadiazoles and Photochemical Generation of Nitrosocarbonyl Intermediates[a]



[a]Reaction conditions: (a) 4-carboxybenzaldehyde, DIC, DMAP, DCM, 48 h; (b) (i) $NH_2OH{\cdot}HCl$, Et_3N, MeOH, 48 h; (ii) NCS, DCM, 2 h; (iii) Et_3N, DCM, 2 h; (c) benzamidoxime, toluene, 48 h; (d) $(EtO)_3P$, benzene, Δ, overnight; (e) KCN, Et_3N, MeOH/THF (1:3), reflux, 2 days; (f) 4-cyanobenzoic acid, DIC, DMAP, THF, 48 h; (g) $NH_2OH{\cdot}HCl$, DIPEA, EtOH, 60 °C, 16 h; (h) benzhydroximoyl chloride, Et_3N, toluene, 48 h; (j) MeOH, *hν*; (k) C_5H_6.

DOI: 10.1021/acscombsci.8b00044
ACS Comb. Sci. 2018, 20, 309−329

Scheme 32. Solid-Phase Synthesis of 1,2,4-Oxadiazoles from a Selenopolystyrene Resin[a]



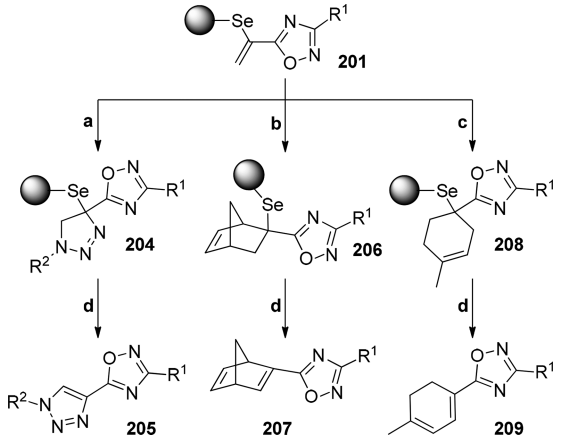
[a]Reaction conditions: (a) $CH_2CHCOOH$, $ZnCl_2$, DCM, 2 h; (b) *t*-BuONa, Et_2O, 12 h; (c) R^2CHNOH, NCS, Et_3N, DCM, 24 h; (d) $R^1C(NH_2)NOH$, DCC, 1,4-dioxane, 90 °C, 15 h; (e) H_2O_2, THF, 0 °C to rt, 1 h.

heterocycles. In the first approach, a 1,3-dipolar cycloaddition of resin **199** with nitrile oxides was performed to afford the resin-bound 3-substituted 4,5-dihydroisoxazol **200**. Resin **200** was then reacted with amidoxime and DCC using Porco's two-step, one-pot condensation to give 1,2,4-oxadiazole resin **202**. In the second approach, the reaction steps from the first approach were reversed, and resin **199** was first reacted with amidoxime in the presence of DCC to give intermediate resin **201** and then reacted with nitrile oxides through a 1,3-dipolar cycloaddition to give 1,2,4-oxadiazole resin **202**. The cleavage from the resin was performed by selenoxide syn-elimination to give the substituted 5-(isoxazol-5-yl)-1,2,4-oxadiazoles **203** in moderate-to-good yields and high purities (>87%). The yields of the products from the first approach were comparably lower (51−55%) than those from the second approach (58−73%); thus, the second strategy was preferable.

Additionally, for the diversity of the method to be expanded, 1,3-dipolar cycloaddition with azides and Diels−Alder reaction with cyclopentadiene and isoprene were performed with intermediate resin **201** to give resin-bound biheteroaryl compounds **204**, **206**, and **208**, respectively (Scheme 33). The release of the products from the polymer support was conducted using H_2O_2 and THF, affording 4-(1,2,4-oxadiazol-5-yl)-1*H*-1,2,3-triazoles **205**, 5-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)-1,2,4-oxadiazoles **207**, and 5-(4-methylcyclohexa-1,3-dien-yl)-1,2,4-oxadiazoles **209** in good yields (56−78%) and purities (>87%).

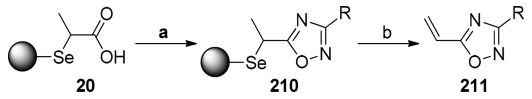
Hu et al. continued their studies and reported the solid-phase synthesis of vinyl-substituted 1,2,4-oxadiazoles using Selene-bound resin (Scheme 34).[102] The synthesis strategy is similar to the synthesis of previously reviewed vinyl-substituted 1,3,4-oxadiazoles (Scheme 6) based on resin-bound *α*-selenopropionic acid **20**. For the synthesis of 1,2,4-oxadiazoles, resin **20** was treated with various amidoximes in the presence of EDC in DMF at 65 °C overnight and additional reflux at 115 °C for 5 h to give cyclized resin **210**. Subsequent syn-elimination of selenoxide afforded 5-vinyl-substituted 1,2,4-oxadiazoles **211** in high yields (>72%) and purities (>90%).

Scheme 33. Solid-Phase Synthesis of 1,2,4-Oxadiazole-Based Biheteroaryls from a Selenopolystyrene Resin[a]



[a]Reaction conditions: (a) NaN_3, R^2I, CuI, proline, LiOH, DMSO, 65 °C, 15 h; (b) cyclopentadiene, ZnI_2, DCM, 12 h; (c) isoprene, ZnI_2, DCM, 12 h; (d) H_2O_2, THF, 0 °C to rt, 1 h.

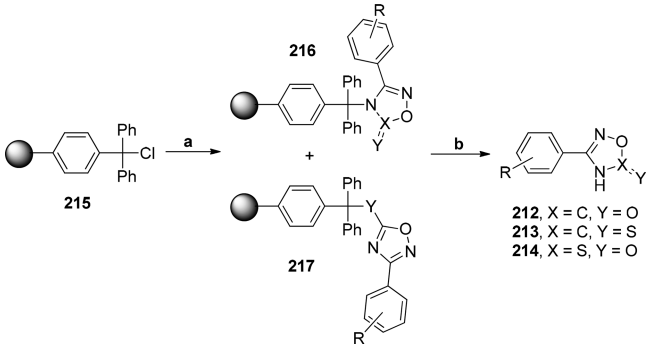
Scheme 34. Solid-Phase Synthesis of Vinyl-Substituted 1,2,4-Oxadiazoles from Resin-Bound *α*-Selenopropionic Acid[a]



[a]Reaction conditions: (a) amidoximes, EDC, DMF, 65 °C, overnight; 115 °C, 5 h; (b) H_2O_2, THF, 0 °C to rt, 1.5 h.

In addition, Charton et al. reported a versatile solid-phase synthesis of 3-aryl-1,2,4-oxadiazolones and analogues.[103] They developed a loading procedure of the 1,2,4-oxadiazolones **212**−**214** on a solid support, such as trityl chloride resin **215** and 4-hydroxymethyl-3-methoxyphenoxybutyric acid benzhydrylamine (HMPB-BHA) resin **218**. First, heterocyclic compounds **212**−**214** were anchored on trityl chloride resin **215** using alkylation conditions (Scheme 35). However, only 3-phenyl-1,2,4-oxadiazole-5-thione **213** was successfully anchored due to the higher nucleophilicity of the sulfur atom (75% yield, 99% purity). In a second attempt to anchor heterocycles on a solid support, HMPB-BHA resin **218** was used under Mitsunobu conditions with PPh_3 and diisopropyl azodicarboxylate (DIAD)

Scheme 35. Loading and Cleavage of Prototypal Compounds 212−214 on Trityl Resin[a]



[a]Reaction conditions: (a) **212**, **213**, or **214**, Et_3N, DMF, 12−24 h; (b) 1−5% TFA in DCM, 2 h.

DOI: 10.1021/acscombsci.8b00044
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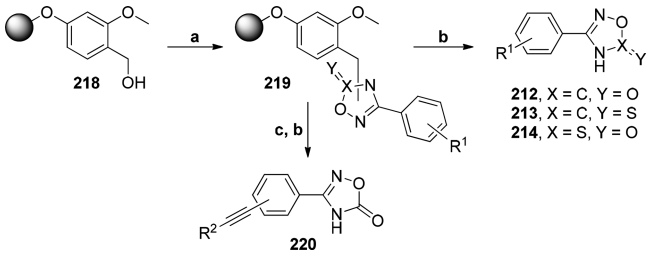
in THF (Scheme 36). Fortunately, the loading on resin **218** was successful, and allowed recovery of the heterocycles in

Scheme 36. Loading and Cleavage of Prototypal Compounds 212−214 on HMPB-BHA Resin[a]



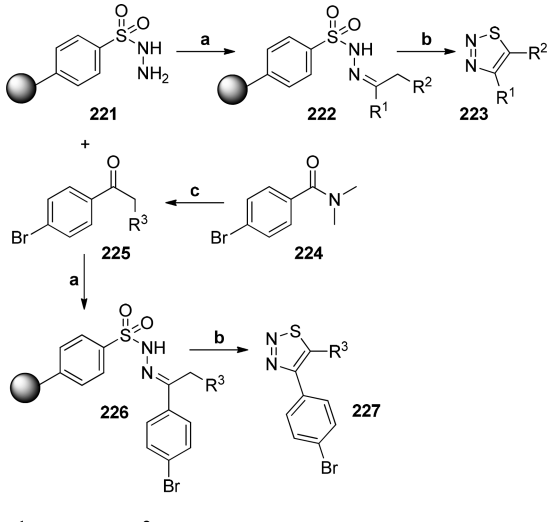
[a]Reaction conditions: (a) **212**, **213**, or **214**, PPh_3, DIAD, THF, 12−24 h; (b) 1−5% TFA in DCM, 3 h; (c) alkyne, $PdCl_2$, CuI, DIPEA, DMF, 3 h.

good yields (45−70%) and high purities (>96%). For the developed utility to be demonstrated, solid-phase Sonogashira coupling was performed on the resin-bound 3-(iodophenyl)-1,2,4-oxadiazol-5(4*H*)-ones **219** with alkynes in the presence of $PdCl_2$, CuI, and DIPEA in DMF with subsequent cleavage from the resin to give (arylethynyl)phenyl-1,2,4-oxadiazol-5(4*H*)-ones **220** in moderate yields (30−37%).

3. Solid-Phase Synthesis of 1,2,3-, 1,2,4-, and 1,2,5-Thiadiazoles. Unlike 1,3,4-thiadiazoles, other thiadiazole isomers have not been studied deeply; thus, there are only a few reports on the solid-phase synthesis of 1,2,3-, 1,2,4-, and 1,2,5-thiadiazoles. The 1,2,3-thiadiazoles can be prepared in solution phase by the following methods: (i) cyclization of hydrazones with thionyl chloride (Hurd−Mori synthesis), (ii) cycloaddition of diazoalkanes onto a C═S bond (Pechmann synthesis), (iii) heterocyclization of α-diazo thiocarbonyl compounds (Wolff synthesis), and (iv) ring transformation of other sulfur-containing heterocyclic compounds. The 1,2,4-thiadiazoles can be prepared from (i) oxidative cyclization of an *N*-thioacyl amidine, (ii) cycloaddition of nitrile sulfides with a nitrile, or (iii) oxidation of thioamides or thioureas. In the case of 1,2,5-thiadiazoles, they can be prepared from 1,2,3-thiadiazoles or an α-aminocarboxamide with sulfur species.[17b]

Hu et al. proposed one of the first thiadiazole solid-phase synthesis strategies.[104] The research group developed "catch and release" and "resin capture" strategies for the synthesis of 1,2,3-thiadiazoles using gel-type polystyrene-sulfonylhydrazide ($PS\text{-}TsNHNH_2$) resin **221** (Scheme 37). For the catch and release strategy, the key intermediate sulfonylhydrozone resin **222** was prepared by treatment of resin **221** with commercially available aromatic and symmetrically aliphatic ketones in the presence of acetic acid in THF at 50 °C for 4 h. The cyclative release from the resin was performed by treatment with thionyl chloride in DCE at 60 °C for 5 h to afford 4,5-disubstituted 1,2,3-thiadiazole derivatives **223** in high yields (79−100%) and purities (>96%). For the resin capture strategy, ketones **225** were prepared separately in solution phase from *N*-methoxy-*N*-methyl-*p*-bromobenzamide **224** with a variety of Grignard reagents, and the reaction mixtures were then quenched with a macroporous polystyrene-sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate. After the capture of ketones **225** by the $PS\text{-}TsNHNH_2$ resin **221**, the resulting product was cleaved from resin **226** using Hurd−Mori conditions and thionyl chloride in THF. The desired products

Scheme 37. Solid-Phase Synthesis of 1,2,3-Thiadiazoles Using $PS\text{-}TsNHNH_2$ Resin[a]

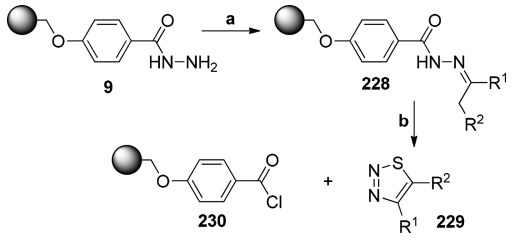


[a]Reaction conditions: (a) $R^1COCH_2R^2$, 10% AcOH, THF, 50 °C, 4 h; (b) $SOCl_2$, DCE, 60 °C, 5 h; (c) (i) R^3CH_2MgX, THF, 0 °C, 3 h; (ii) MP-TsOH.

were obtained in moderate-to-high yields (48−98%) and purities (>71%).

Liu et al. presented traceless solid-phase synthesis of 1,2,3-thiadiazole derivatives.[105] Previously, the group reported 1,3,4-thiadiazole synthesis using acylhydrazine intermediate resin **9** (Scheme 4).[69] In continuation of these studies, the solid-phase synthesis of 1,2,3-thiadiazoles was developed by treatment of resin **9** with ketones in the presence of AcOH in EtOH to obtain resin **228** (Scheme 38). The cleavage from the resin was

Scheme 38. Traceless Solid-Phase Synthesis of 1,2,3-Thiadiazoles[a]



[a]Reaction conditions: (a) $R^1COCH_2R^2$, AcOH, EtOH, reflux, 24 h; (b) $SOCl_2$, DCM, 20 h.

conducted using Hurd−Mori cyclative release by thionyl chloride in DCM at rt for 20 h to afford 1,2,3-thiadiazole derivatives **229** in high yields (78−93%) and purities (>85%). Additionally, they proposed the recycling methodology of formed resin **230** back to acylhydrazine resin **9**.

Ryu et al. reported the solid-phase parallel synthesis of 5-amino- and 5-amido-1,2,4-thiadiazole derivatives via the cyclization of a carboxamidine thiourea intermediate (Scheme 39).[106] The already mentioned BOMBA resin **58** was converted to the isothiocyanate-terminated resin **59** using thiophosgene in the presence of Et_3N in DCM at 0 °C. Next, resin **59** was reacted with various carboxamidines in the presence of DBU in DCM to give resin-bound carboxamidine thiourea intermediate **231**, which was then converted to 1,2,4-thiadiazole resin **232**

DOI: 10.1021/acscombsci.8b00044
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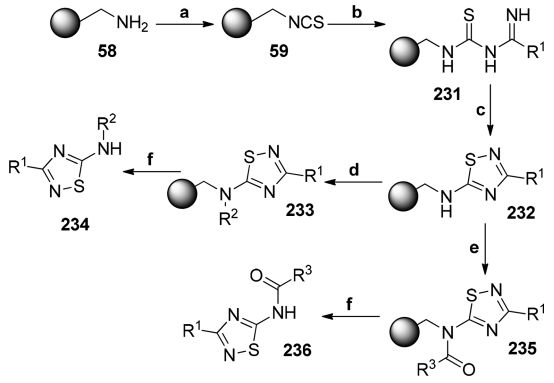
Scheme 39. Solid-Phase Synthesis of 1,2,4-Thiadiazoles[a]

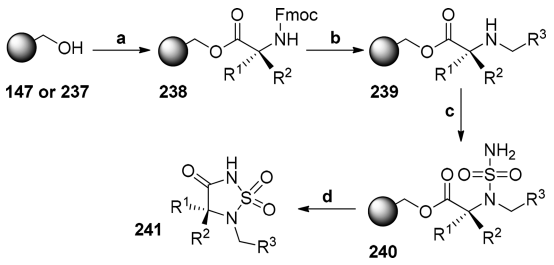


[a]Reaction conditions: (a) $CSCl_2$, Et_3N, DCM, 0 °C to rt, 5 h; (b) carboxamidines, DBU, DCE, 60 °C, 16 h; (c) *p*-TsCl, Et_3N, DCE, 60 °C, 8 h; (d) alkyl halide, NaH, THF, 60 °C, 24 h; (e) acid chloride, LiHMDS, DMAP, THF, 60 °C, 24 h; (f) TFA, DCM, 4 h.

using *p*-TsCl as a dehydrating agent. 1,2,4-Thiadiazole resin **232** was functionalized with alkyl halides and acid chlorides under standard reaction conditions to result in resins **233** and **235**, respectively. The release from the supporting resin was conducted using the TFA/DCM cleavage cocktail to afford *N*-alkyl- and *N*-acylamino-1,2,4-thiadiazoles **234** and **236**, respectively, in moderate yields (6−33%) and high purities (>91%).

Finally, Albericio et al. reported the solid-phase synthesis of 2-unsubstituted 1,2,5-thiadiazolidin-3-one 1,1-dioxides (sulfahydantoins) from Fmoc-protected amino acids and aromatic aldehydes (Scheme 40).[107] The synthesis was accomplished on

Scheme 40. Solid-Phase Synthesis of Sulfahydantoins[a]



[a]Reaction conditions: (a) (i) Fmoc-NHCR^{1}R^{2}CO$_2$H, DIC, DMAP, DCM/DMF (5:1), 2 h; (ii) piperidine/DMF (1:4), 20 min; (b) (i) R^{3}CH$_2$CHO, AcOH, DCM/TMOF (1:1), 5 h; (ii) $NaCNBH_3$, DCM/TMOF (1:1), 6 h; (c) H_2NSO_2Cl, 2,4,6-collidine, DCM, 4 h; (d) DBU, DCM, 5 h.

Wang resin **147** and MBHA resin **237** beginning with the coupling with Fmoc-protected amino acids under standard DIC/DMAP conditions with subsequent deprotection with piperidine in DMF to afford resin **238**. Next, reductive alkylation of resin **238** was conducted with benzaldehydes to give resin **239**. Further treatment of resin **239** with chlorosulfamic acid in the presence of 2,4,6-collidine resulted in intermediate resin **240**, which could undergo cyclative cleavage using DBU in DCM to afford the desired sulfahydantoins in moderate yields (7−31%) and good purities (>75%).

CONCLUSIONS

The oxadiazoles and thiadiazoles are important core skeletons for drug design. Therefore, many researchers have shown interest in the rapid, easy, and eco-friendlier synthetic approaches. In this respect, solid-phase synthesis techniques are attractive because they can conduct rapid and simple access to the libraries of compounds. This review has summarized solid-phase synthesis strategies of the oxadiazole and thiadiazole derivatives. Several classic solution-phase synthesis methodologies have been reported so far, and some of the methods were modified and transferred on solid phase with new reaction conditions and versatile structures of the obtained compounds, which is important in drug development. Various polymer supports were used in the syntheses, including Merrifield resin, Rink amide resin, Wang resin, JandaJel, and so forth. Compounds were synthesized not only on solid supports but also using polymer-bound reagents in the solution-phase synthesis. Compared to other isomers, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were better studied; thus, new effective solution-phase synthesis methodologies, as well as diverse solid-phase synthesis strategies, have been reported over the years. The 1,2,4-oxadiazoles are also well-known isomers and have several solid-phase reports. However, we could not find any solid-phase synthesis records of 1,2,3- and 1,2,5-oxadiazoles, probably due to the difficulties related to the synthesis of the core. In contrast with the oxadiazoles, the thiadiazole isomers are less discovered, and there are only a few reports of solid-phase synthesis approaches.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Basic Science Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2016R1D1A1B04932654) and the Sabbatical Research Program of Dongguk University in Seoul, Korea.

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DOI: 10.1021/acscombsci.8b00044
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