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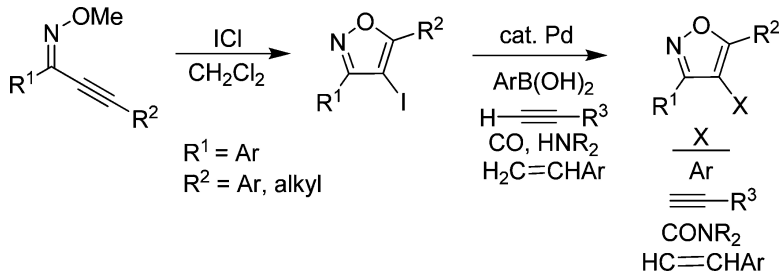

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Solution Phase Synthesis of a Diverse Library of Highly Substituted Isoxazoles

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The iodocyclization of *O*-methyloximes of 2-alkyn-1-ones affords 4-iodoisoxazoles, which undergo various palladium-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles. The palladium-catalyzed processes have been adapted to parallel synthesis utilizing commercially available boronic acid, acetylene, styrene, and amine sublibraries. Accordingly, a diverse 51-member library of 3,4,5-trisubstituted isoxazoles has been generated.

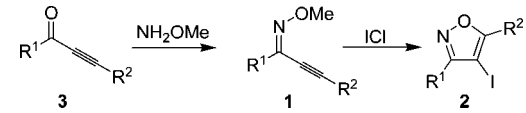
Introduction

Low molecular weight nitrogen-containing heterocycles are securing their place among the most highly recognized pharmacophores.[1] Among them, the isoxazole scaffold is of particular interest, since it is known to exhibit a broad range of biological activity.[2] Isoxazoles have also had a significant impact as intermediates in the synthesis of various natural products.[3] Consequently, isoxazoles are prized as potential drug candidates and biological probes. There have been several reports relating to the synthesis of functionalized isoxazoles by combinatorial techniques,[4] although the use of 4-iodoisoxazoles as the key intermediate for library generation is thus far unreported. Many of the reported libraries have been limited to the preparation of disubstituted isoxazoles. Additionally, functionalization at the C4 position of the isoxazole core, with respect to library generation, has previously met with limited success. Until recently, restricted access to 4-haloisoxazoles, by a route involving mild reaction conditions, has prevented them from being an important intermediate for library generation. The halogenation of isoxazoles at the C4 position generally requires the use of high temperatures and harsh acids.[5]

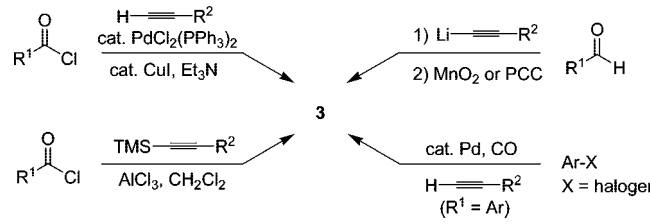
Previous work in our laboratory has demonstrated that the electrophilic cyclization of *Z*-2-alkyn-1-one *O*-methyl oximes (**1**), using ICl, provides a mild and selective route to 3,5-disubstituted-4-iodoisoxazoles (**2**) (Scheme 1).[6] The requisite 2-alkyn-1-ones (**3**) required for this methodology can be readily synthesized by established chemistry utilizing commercially available starting materials (Scheme 2).[7]

We have previously demonstrated the significance of this methodology by reporting individual examples of Sonogashira,[8] Suzuki-Miyaura,[9] Heck,[10] and carbonylative amidation cross-coupling reactions,[11] which provide the corresponding 3,4,5-trisubstituted isoxazoles in good yields, including the highly potent COX-2 inhibitor valdecoxib (**4**) (Scheme 3).[12] With optimized conditions in hand for each of these processes, we wished to adapt

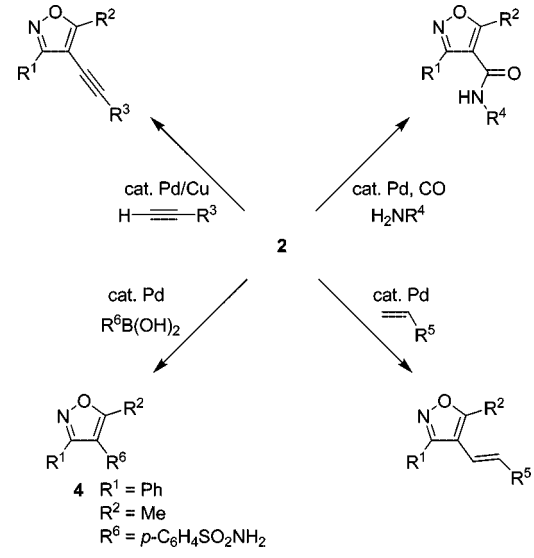
Scheme 1



Scheme 2



Scheme 3



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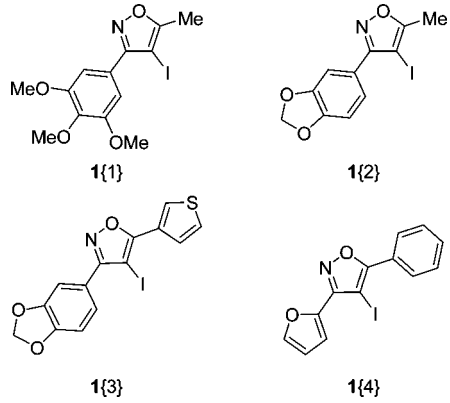


Figure 1. 4-Iodoisoxazole sublibrary.

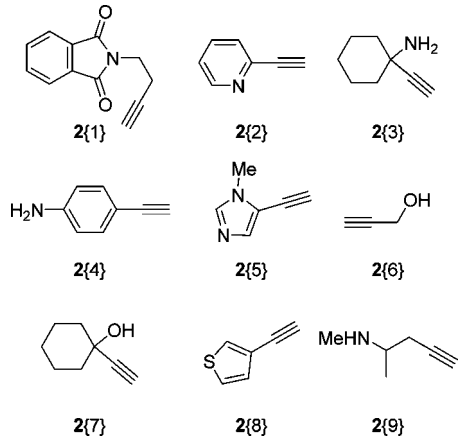


Figure 2. Terminal acetylene sublibrary.

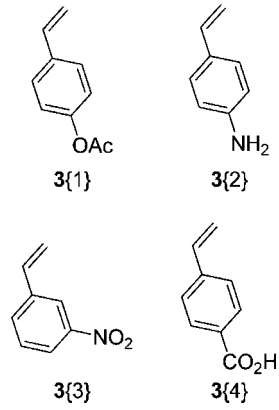


Figure 3. Styrene sublibrary.

these reactions to library generation. Herein, we report the success of this objective.

Results and Discussion

Our 4-iodoisoxazole synthesis has previously been demonstrated to tolerate, but not be limited to, alkyl and aryl groups at the R^1 or R^2 positions of the isoxazole core.[6] During our initial study, we found that employing of *Z-O*-methyloximes was essential to the success of our methodology, since the corresponding *E-O*-methyloximes proved ineffective in the electrophilic cyclization process. Since bulky groups at the R^1 position provided the highest yields of the necessary *Z-O*-methyloximes required for our 4-iodoisoxazole synthesis, R^1 was restricted to aryl groups for library generation. Since R^2 substituents had less of an effect on the outcome of our methodology, there was no need to adhere to strict guidelines when choosing R^2. Accordingly,

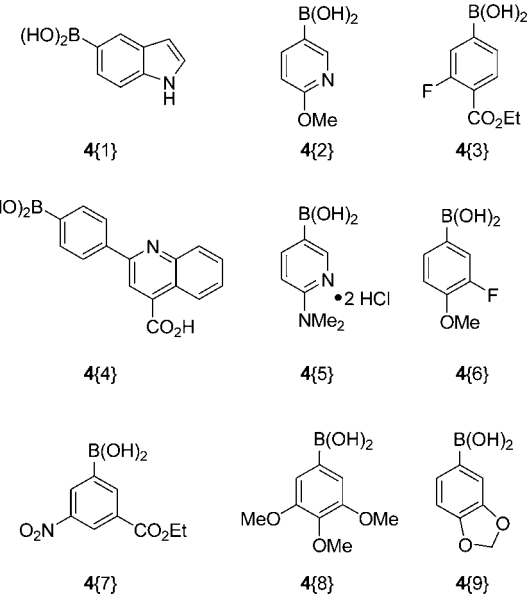


Figure 4. Boronic acid sublibrary.

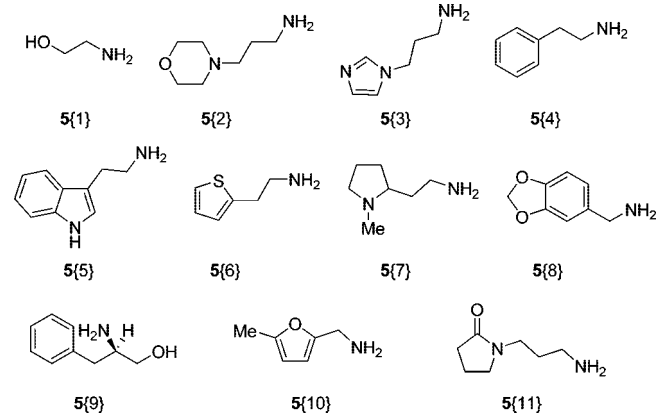
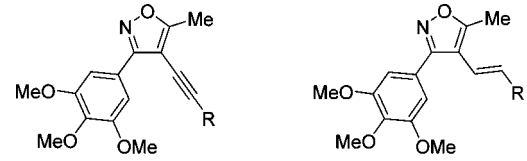


Figure 5. Primary amine sublibrary.

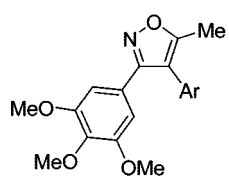
Table 1. Library Data for Compounds **6**{1−13}



compound	R	yield[a] (%)	purity[b] (%)
6{1}	2-ethylphthalimide	40	94
6{2}	2-pyridinyl	30	97
6{3}	1-amino-1-cyclohexyl	42	95
6{4}	4-$H_2NC_6H_4$	62	99
6{5}	1-methyl-1H-imidazo-5-yl	83	95
6{6}	CH_2OH	67	97
6{7}	1-hydroxy-1-cyclohexyl	59	99
6{8}	3-thiophenyl	75	97
6{9}	2-(*N*-methyl)propyl	50	97
6{10}	4-$AcOC_6H_4$	60	94
6{11}	4-$H_2NC_6H_4$	67	93
6{12}	3-$O_2NC_6H_4$	73	95
6{13}	4-$HO_2CC_6H_4$	8	87

[a] Isolated yield after preparative HPLC. [b] UV purities determined at 214 nm after preparative HPLC.

Table 2. Library Data for Compounds **6**{14−43}



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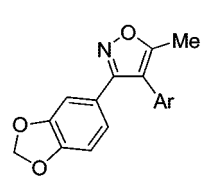
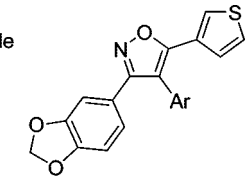
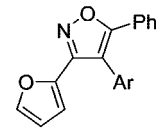


6{21-27}



6{28-35}



6{36-43}

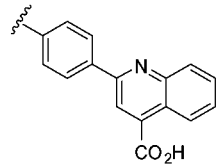
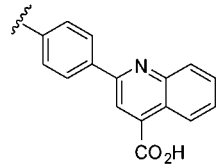
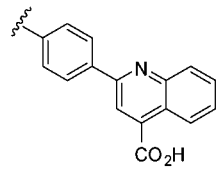
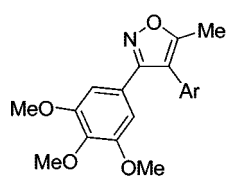
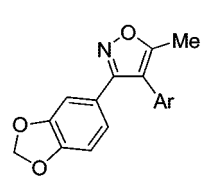
compound	Ar	yield[a] (%)	purity[b] (%)
6{14}	5-indolyl	24	92
6{15}	6-methoxy-3-pyridinyl	29	95
6{16}	4-EtO_2C-3-FC_6H_4	53	96
6{17}		5	87
6{18}	6-(*N*,*N*-dimethyl)-3-pyridinyl	22	94
6{19}	4-MeO-3-FC_6H_4	58	97
6{20}	3-MeO_2C-5-$O_2NC_6H_4$	44	97
6{21}	5-indolyl	51	92
6{22}	6-methoxy-3-pyridinyl	26	95
6{23}	4-EtO_2C-3-FC_6H_4	26	97
6{24}		0	
6{25}	6-(*N*,*N*-dimethyl)-3-pyridinyl	7	100
6{26}	4-MeO-3-FC_6H_4	46	88
6{27}	3-MeO_2C-5-$O_2NC_6H_4$	0	
6{28}	5-indolyl	79	97
6{29}	6-methoxy-3-pyridinyl	81	95
5{30}	4-EtO_2C-3-FC_6H_4	73	99
6{31}		57	94
6{32}	6-(*N*,*N*-dimethyl)-3-pyridinyl	85	96
6{33}	4-MeO-3-FC_6H_4	73	99
6{34}	3,4,5-$(MeO)_3C_6H_4$	44	91
6{35}	5-indolyl	75	96

Table 2. continued



6{14-20}



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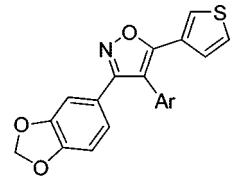
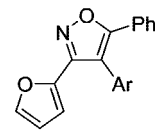
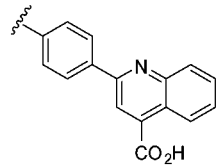


6{28-35}



6{36-43}

compound	Ar	yield[a] (%)	purity[b] (%)
6{36}	6-methoxy-3-pyridinyl	16	91
6{37}	4-EtO_2C-3-FC_6H_4	64	98
6{38}		7	100
6{39}	6-(*N*,*N*-dimethyl)-3-pyridinyl	20	92
6{40}	4-MeO-3-FC_6H_4	60	99
6{41}	3-EtO_2C-5-$O_2NC_6H_4$	0	
6{42}	3,4,5-$(MeO)_3C_6H_4$	53	99
6{43}	3,4-$(OCH_2CH_2O)C_6H_3$	44	99

[a] Isolated yield after preparative HPLC. [b] UV purities determined at 214 nm after preparative HPLC.

we chose a subset of various 4-iodoisoxazoles which could be synthesized from readily available starting materials (Figure 1).

Isoxazoles **1**{1−4} were selected because their synthesis is straightforward and the oxygen heteroatoms provide desired polarity in the resulting library.

The alkyne sublibrary, used for Sonogashira cross-coupling, was chosen based on commercially available, heteroatom-containing acetylenes that could provide hydrogen bond donors and/or acceptors (Figure 2).

A small styrene sublibrary for Heck cross-coupling was chosen to demonstrate vinylic functionalization. However, only a few functionally diverse styrenes were available from commercial sources (Figure 3). We avoided the use of better Michael acceptors, such as acrylates or acrylonitriles, since the resulting Heck products would also be excellent Michael acceptors and thus undesirable for subsequent pharmaceutical applications.

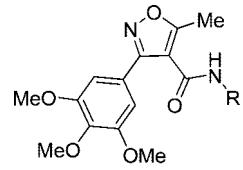
Commercially available boronic acids, for Suzuki-Miyaura cross-coupling, were chosen based on their diverse functionality (Figure 4). 5-Indoleboronic acid **4**{1} was chosen because the resulting cross-coupling products could generate druglike scaffolds with potentially positive physiochemical properties. Arylboronic acids **4**{3} and **4**{6} were chosen because the resulting cross-coupling products would contain fluorine atoms. Organofluorine compounds are of considerable interest because of their versatile applications in industry and medicine.[13] Other boronic acids within the sublibrary were chosen because they contain heterocycles and polar functionality that would incorporate druglike moieties in the resulting cross-coupling products.

Primary amines were chosen as a sublibrary for palladium-catalyzed amide formation, because the resulting nitrogen-containing products would enable us to make compounds with potentially attractive druglike features, including molecular weight, solubility, and molecular polarizability. Amines **5**{1−11} were chosen to represent compounds found in natural products and derivatives of substances known to possess biological activity (Figure 5).

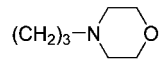
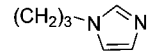
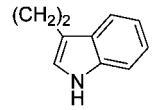
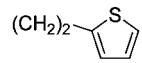
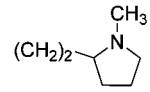
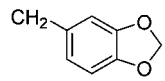
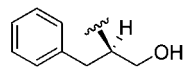
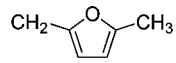
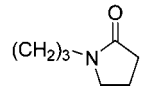
To ease the transition from our isoxazole methodology to library generation, we wished to preserve the protocols we had originally employed for the cross-coupling of 4-iodoisoxazoles with terminal acetylenes, styrenes, boronic acids, and amines.[6b] With these preliminary findings, we proceeded to prepare a diverse library of 3,4,5-trisubstituted isoxazoles as outlined in Scheme 3. The crude products were analyzed by LC/MS, followed by purification by preparative HPLC.

The results of the library synthesis are summarized in Tables 1–3. The crude products were subjected to preparative HPLC, and purities in the range of 87−100% were achieved after purification. Most of the reactions proceeded well, with the exception of the Heck reaction of 4-vinylbenzoic acid. In the Suzuki−Miyaura reaction of boronic acids **4**{5} and **4**{7}, poor or no yield of the desired product was observed. Palladium-catalyzed amide formation using carbon monoxide and primary amines proceeded smoothly and provided the corresponding amides in satisfactory yields with high purities.

Table 3. Library Data for Compounds **6**{44−54}



6{44-54}

compound	R	yield[a] (%)	purity[b] (%)
6{44}	$(CH_2)_2OH$	24	99
6{45}		44	99
6{46}		50	100
6{47}	$(CH_2)_2Ph$	58	96
6{48}		39	97
6{49}		79	99
6{50}		65	96
6{51}		40	99
6{52}		27	99
6{53}		80	99
6{54}		69	99

[a] Isolated yield after preparative HPLC. [b] UV purities determined at 214 nm after preparative HPLC.

Table 4. In silico Parameters for Gauging Oral Availability/ Druglikeness

	mean	st dev	range
clog P	3.13	1.40	−0.01–6.87
mol. weight	380.8	46.4	292.3–518.5
H-bond acceptors	6.00	1.13	3–9
H-bond donors	0.92	0.73	0–2
rotatable bonds	5.14	1.67	2–8

Out of a total of 54 palladium-catalyzed processes attempted, only three failed completely.

Because of our interest in synthesizing heterocycles for use in high-throughput screening projects, an in silico evaluation of library members was carried out to determine their agreement with Lipinski's "rule of five" and Veber's rules.[15] Molecular weight, clog P, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were either specified or calculated for each of the library members using the SYBYL[16] program (Table 4). Most of the isoxazole library members were highly Lipinski compliant. In fact, 96% of the library members are entirely compliant with Lipinski rules and only compound **6**{31} had multiple violations, including molecular weight and clog P.

In conclusion, the preparation and subsequent palladium-catalyzed reactions of 4-iodoisoxazoles with various cross-coupling partners has allowed for simple construction of a 51-member library of 3,4,5-trisubstituted isoxazoles. The

average yield of the library was 49% and the average purity after preparative HPLC was 96%.

Acknowledgment. We would like to thank Frank Schoenen for his useful discussions and David Hill at the University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development for obtaining the library NMR spectra. We thank the National Institute of General Medical Sciences (R01 GM070620 and R01 GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (P50 GM069663) for support of this research; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts; and Frontier Scientific and Synthonix for donations of boronic acids.

Supporting Information Available. Experimental details and characterization of a representative 20 library members, including full ^{1}H and ^{13}C NMR spectra and conditions for the high throughput liquid chromatography purification. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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