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RESEARCH ARTICLE

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# Triazole-Containing Isothiazolidine 1,1-Dioxide Library Synthesis: One-Pot, Multi-Component Protocols for Small Molecular Probe Discovery

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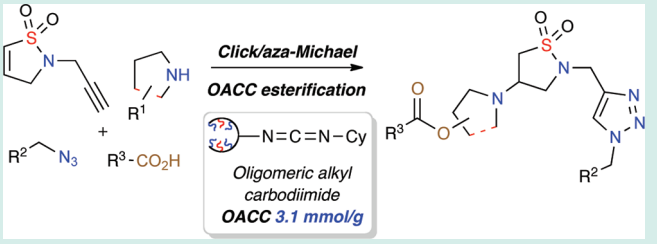
Supporting Information

**ABSTRACT:** The construction of two libraries of triazole-containing isothiazolidine 1,1-dioxides is reported utilizing either a one-pot click/aza-Michael or click/OACC esterification protocol. One core dihydroisothiazole 1,1-dioxide scaffold was prepared rapidly on multigram scale via ring-closing metathesis (RCM) and was subjected to a one-pot multicomponent click/aza-Michael protocol with an array of amines and azides for the generation of a 180-member triazole-containing isothiazolidine 1,1-dioxide library. Alternatively, three daughter scaffolds were generated via the aza-Michael of three amino alcohols, followed by a one-pot, multicomponent click/esterification protocol utilizing a ring-opening metathesis polymerization (ROMP)-derived coupling reagent, oligomeric alkyl carbodiimide (OACC) to generate a 41-member library of triazole-containing isothiazole 1,1-dioxides.




**KEYWORDS:** triazole-containing isothiazolidine 1, 1-dioxide, sultams, one-pot, aza-Michael, RCM, ROMP

## 1. INTRODUCTION

The need for discovery of new pharmaceutical leads and small molecule probes has led to efforts focusing on the advancement of current high-throughput screening and the corresponding small molecule screening collections. This effort has been driven by the development and emergence of methods, protocols, and technologies to access diverse collections of small molecules in a rapid fashion.[1] Sultams (cyclic sulfonamide analogues) have surfaced in recent years as important targets in drug discovery because of their extensive chemical and biological profiles.[2] In this regard, $\beta$-amino sultams and their corresponding sulfonate analogues are a relatively new chemotype that has shown interesting biological properties. Such reports include the inhibition of HIV-1 replication and antibacterial activity (Figure 1).[3]

Building on these aforementioned reports, it was envisioned that a library of $\beta$-amino sultams, specifically triazole-containing isothiazolidine 1,1-dioxides, could be rapidly generated via a facile one-pot click/aza-Michael diversification protocol of ring-closing metathesis (RCM)-derived dihydroisothiazole 1,1-dioxide core scaffold **2** with a series of amines, azides and acids (Figure 2).

Utilizing RCM,[4] simple 5-, 6-, and 7-membered sultam derivatives from the corresponding allyl and vinyl sulfonamides were readily accessed.[5] In the cases of RCM with vinyl sulfonamides, the corresponding sultam retains the $\alpha,\beta$-unsaturated functionality incorporated within the cycle for diversification utilizing an aza-Michael protocol. Aza-Michael reactions are efficient pathways that, historically, have been broadly utilized to access a variety of heterocycles.[6] Specifically, the hetero-Michael reaction has been utilized as an efficient cyclization protocol to access a variety of sultam motifs leading to the proposed triazole-containing isothiazolidine 1,1-dioxide library.[7]

## 2. RESULTS AND DISCUSSION

The construction of isothiazolidine 1,1-dioxides libraries was envisioned by the diversification of core dihydroisothiazole 1,1-dioxide core scaffolds via a one-pot, multicomponent protocol pairing an aza-Michael diversification reaction with other orthogonal reaction pathways. To this effect, the corresponding core scaffold 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **2** was rapidly generated on multigram scale via a 3-step sulfonylation, RCM, propargylation protocol (Scheme 1).[8,9] Notably, the addition of metathesis catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh; cat-**B**],[9,10] in 5 equal portions of 0.5 mol % (total 2.5 mol %) every 30 min was key to maintaining the observed high conversion of the RCM cyclization.

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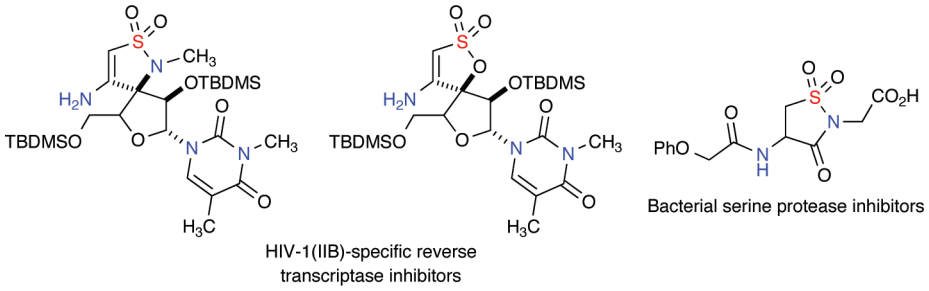



**Figure 1.** Biologically active $\beta$-amino sultams and sulfonates.

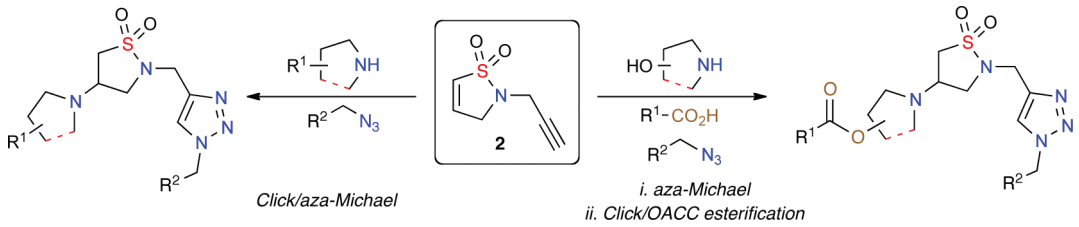



**Figure 2.** One-pot, multicomponent synthesis of triazole-containing isothiazole 1,1-dioxides via orthogonal reactions.

**Scheme 1. Gram Synthesis of Core 2-(Prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-Dioxide 2 via RCM**

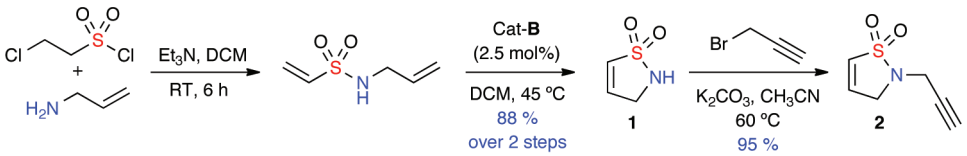
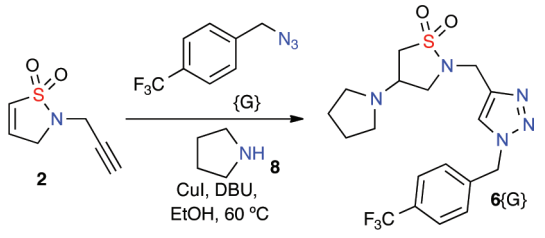



**Table 1. Optimization of One-Pot Click/aza-Michael Reaction Conditions**




| entry[a] | azide {G} (equiv) | amine **6** (equiv) | CuI (mol %) | DBU (mol %) | yield (%) |
|---|---|---|---|---|---|
| 1 | 2 | 2 | 10 mol % | 10 mol % | 62% |
| 2 | 2 | 2 | 30 mol % | 10 mol % | 96% |
| 3 | 1 | 1 | 30 mol % | 10 mol % | 78% |
| 4 | 2 | 1.2 | 30 mol % | 10 mol % | 95% |
| **5** | **2** | **1.2** | **30 mol %** | **10 mol %** | **96%** |

[a] Reactions carried out utilizing **2** (50 mg, 0.32 mmol, 1 equiv) in 0.5 M EtOH at 60 °C for 12 h.

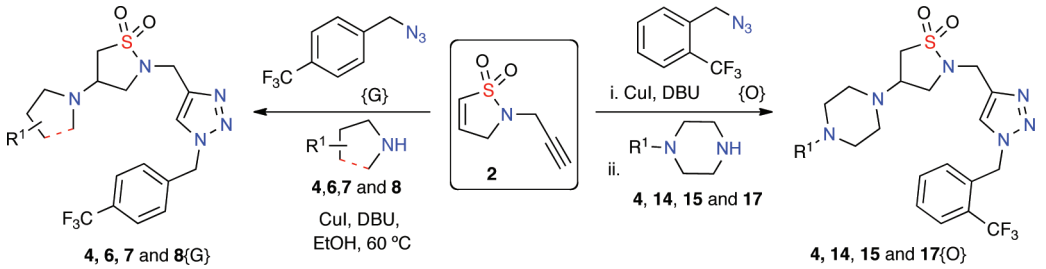
With the desired core sultam **2** in hand, initial efforts focused on the diversification of the core via solely an aza-Michael or click reaction.[8] After successful diversification of **2** utilizing either reactions in high yield, the combination of both reactions in a one-pot protocol was investigated. In this regard, the one-pot click/aza-Michael protocol with azide {G} and pyrrolidine **6** was investigated (Table 1). Initial efforts combined both reaction conditions into the same pot (Table 1, entry 1) yielding the desired product in 62% yield. This yield was improved to 96% after increasing the CuI catalyst load to 30 mol % (Table 1, entry 2), while additional optimization led to the use of lower equivalents of amine without affecting yield (Table 1, entry 5).

With these optimized conditions in hand, a validation library was investigated for the diversification of dihydroisothiazole 1,1-dioxide **2** with a variety of 2° amine nucleophiles (Table 2). Reactions were carried out in 1-dram vials using reaction blocks, whereby crude reaction mixtures were diluted in EtOAc, filtered through a $SiO_2$ SPE, and subjected to a QC check, followed by purification via automated mass-directed LCMS.

With the successful synthesis of the 8-member validation library, two libraries **A** and **B** were proposed for the synthesis of 180-triazole-containing isothiazole 1,1-dioxides derivatives via the diversification of dihydroisothiazole 1,1-dioxide **2** utilizing amines (**3**−**17**) and azides {A−R} (Figure 3).

**Library Design.** For all three libraries A, B, and C, a *full matrix* library was designed using in silico analysis, literature precedence, and observed synthetic results.[10] A virtual library incorporating all possible building block combinations of azides, 2° amines and acids (library C) was constructed for each scaffold (**2**, **18**, **19**, and **20**) (Figure 4). Physico-chemical property filters were applied, guiding the elimination of undesirable building blocks that led to

**Table 2. Library Prototype Utilizing Dihydroisothiazole 1,1-Dioxide 2**




| entry[a] | yield | final purity[c] | mass | entry[b] | yield | final purity[c] | mass |
|---|---|---|---|---|---|---|---|
| **4**{G} | 52% | 99% | 89.3 mg | **4**{O} | 43% | 100% | 22.9 mg |
| **6**{G} | 45% | 99% | 75.4 mg | **14**{O} | 41% | 98% | 22.3 mg |
| **7**{G} | 42% | 92% | 56.2 mg | **15**{O} | 40% | 97% | 19.4 mg |
| **8**{G} | 47% | 99% | 63.9 mg | **16**{O} | 43% | 98% | 22.3 mg |

[a] Reaction conditions: Dihydroisothiazole 1,1-dioxide **2** (50 mg, 1 equiv), azide (2 equiv), amine (1.2 equiv), CuI (30 mol %), DBU (10 mol %), dry EtOH (0.5 M), 60 °C, 12 h. [b] Reaction conditions: Dihydroisothiazole 1,1-dioxide **2** (20 mg, 1 equiv), azide (2 equiv), amine (1.2 equiv), CuI (30 mol %), DBU (10 mol %), dry EtOH (0.5 M), 60 °C, 12 h. [c] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). Purity was determined by HPLC with peak area (UV) at 214 nm and % rounded up to nearest 1%.

products with undesirable in-silico properties.[11] These metric filters included standard Lipinski Rule of 5 parameters (molecular weight <500, ClogP <5.0, number of H-acceptors <10, and number of H-donors <5), in addition to consideration of the number of rotatable bonds (<5) and polar surface area. Absorption, distribution, metabolism, and excretion (ADME) properties were calculated along with diversity analysis using standard H-aware 3D BCUT descriptors comparing against the MLSMR screening set (ca. 7/2010; ~330,000 unique chemical structures). Guided by this library design analysis, the corresponding amines **3**−**17**, azides {A−R} and acids **21**−**25** and sultams (**2**, **18**−**20**) (Figures 3 and 4) were chosen to generate 234 proposed sultams (libraries A, B, and C).

**Library A and B.** Utilizing the optimized conditions, library **A** (132-member) was designed and generated utilizing azides **A**−**L** with amines **3**−**13** via a one-pot click/aza-Michael transformation. Library **B** (48-member) was also generated utilizing azides **A**−**L** with piperazines **14**−**17** via a sequential 2-step click/aza-Michael protocol, instead of the previously used one-pot method. This 2-step sequence was necessary to efficiently remove the Cu catalyst from the crude material without the need of an aqueous workup because of increased affinity for the $SiO_2$ SPE of the corresponding final compounds bearing both a triazole and piperazine moiety. Overall, all 180 triazole-containing isothiazole-1,1-dioxide members of library **A** and **B** were successfully generated, with 167 out of the 180 compounds possessing >90% final purity after purification by automated mass-directed LCMS (Scheme 2).[12]

Within the 132-member library **A** is a unique set of 12 *bis*-triazole-containing isothiazole 1,1-dioxides **13**{A−L} which were generated through a *bis*-click/aza-Michael because of the use of *N*-methyl propargyl amine **13** as the Michael component in the presence of 2 equiv of the corresponding azide (Scheme 3).

**Library C.** Building on the synthesis of 180-member triazole-containing isothiazole 1,1-dioxides, library **C**, a 90-member compound set of derivatives was investigated. This involved the synthesis of three daughter scaffolds (**18**, **19**, and **20**, Figure 4) synthesized from dihydroisothiazole 1,1-dioxide **2**, which underwent diversification via a one-pot procedure click/oligomeric alkyl cyclohexylcarbodiimide (OACC) esterification to generate the desired 90-membered library (Scheme 4).

Key to the combination of these orthogonal reaction pathways is the utilization of an immobilized, soluble ring-opening metathesis polymerization (ROMP)-derived coupling reagent OACC.[13] This high load reagent allows for efficient coupling of a variety of acids with **18**, **19**, or **20**, followed by facile removal via a simple precipitation/filtration protocol.

Initially, the three daughter isothiazole 1,1-dioxide scaffolds **18**, **19**, and **20** were generated via aza-Michael of the corresponding amino alcohols with dihydroisothiazole 1,1-dioxide **2** in an efficient multigram synthesis. With these core isothiazole-1,1-dioxide (**18**, **19**, and **20**) scaffolds prepared, a 90-member library was designed utilizing a combination of **18**, **19**, and **20** with azides **M**−**P** and acids {21−25} (Figure 4).

Using the aforementioned method, a one-pot click/OACC esterification protocol for the synthesis of library **C** was achieved utilizing 1.2 equiv of acid {21−25}, azide (2 equiv), OACC (1.5 equiv), CuI (30 mol %), DBU (10 mol %), and anhydrous $CH_2Cl_2$ (Table 3). Reactions were carried out at 50 °C for 12 h, whereby upon completion the crude reactions were diluted, filtered, and concentrated. Utilizing these conditions an initial validation set of isothiazolidine-1,1-dioxides was investigated to evaluate the reaction conditions (Table 3).

Upon completion, the validation set was diluted in EtOAc to precipitate the spent oligomer, followed by filtration through a $SiO_2$ SPE and concentration. All samples were purified by column chromatography, characterized, and then submitted to purification by reverse-phase automated mass-directed LCMS.[14] Despite their stability when isolated after standard chromatography, it was observed that esters generated with acids **21** and **23** underwent complete hydrolysis during automated mass-directed LCMS. Analysis indicated that after successful purification, hydrolysis occurred during the final step of removal of the solvent utilized ($CH_3CN$, $H_2O$, DMSO, and $NH_4OH$). Because of this observation, library **C** was redesigned removing acids **21** and **23** to propose a 54-member library (Scheme 5).

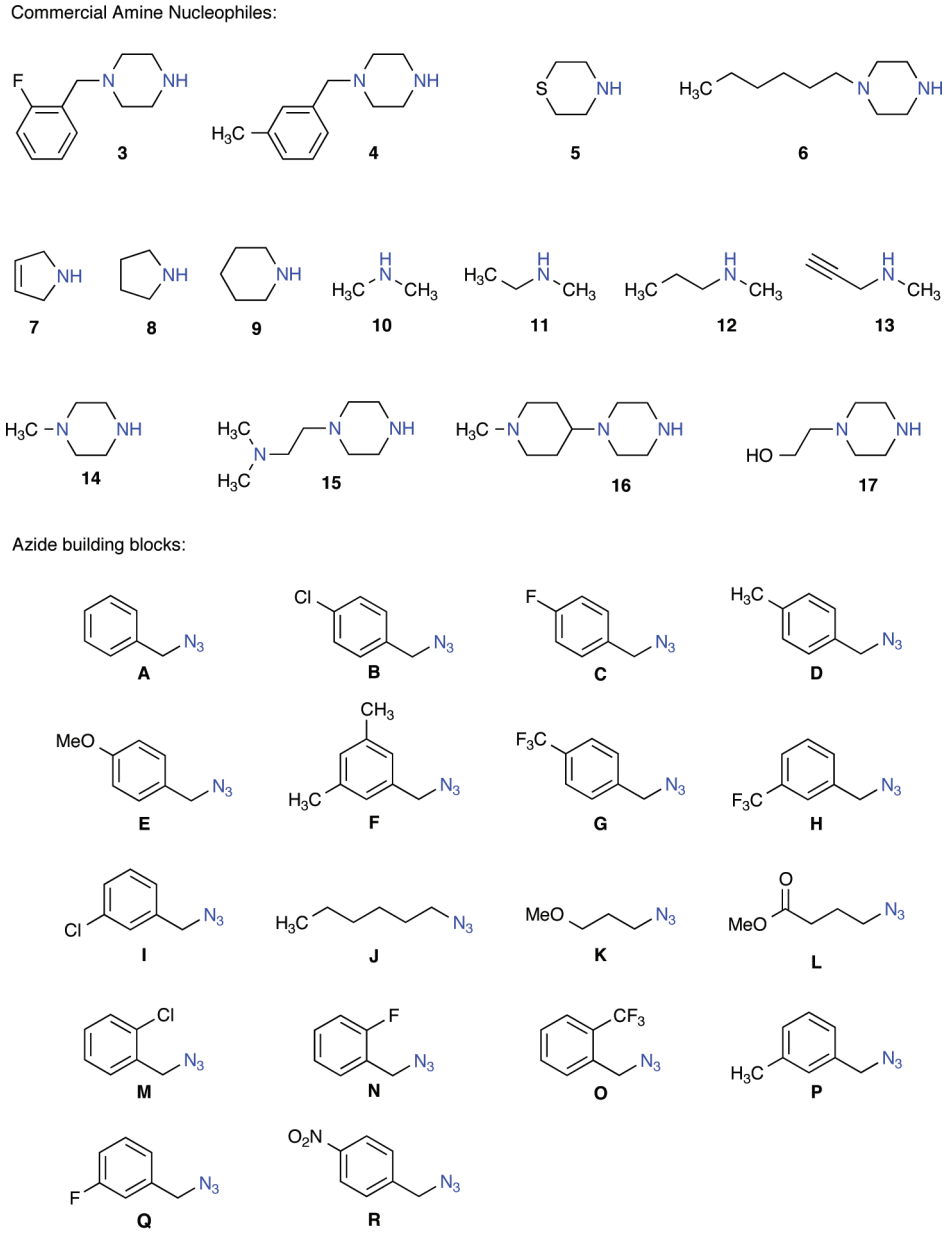



**Figure 3.** Amine (**3**−**17**) and Azide {A−R} library building blocks.

Under these conditions, 41 out of 54 compounds were successfully isolated >90% purity after purification by automated mass-directed LCMS. Crude reaction analysis indicated that all 54 reactions worked; however, it is proposed that the failed reactions and low yields observed were due to hydrolysis of the desired product in the final stages of purification.

## 3. CONCLUSION

In conclusion, three libraries of triazole-containing isothiazolidine 1,1-dioxides were prepared utilizing either a one-pot click/aza-Michael or click/esterification protocol for utilization in high throughput screening (HTS) collections. One core dihydroisothiazole 1,1-dioxide scaffold was prepared on multigram scale via RCM and rapidly diversified via a one-pot multicomponent click/aza-Michael protocol to generate a 180-triazole-containing isothiazole 1,1-dioxide library (**A** and **B**). All 180 compounds were successfully generated, with 167 possessing >90% final purity after purification by automated mass-directed LCMS. Building on this success, a 41-member library **C** of triazole-containing isothiazole 1,1-dioxide library was prepared via a one-pot, click/OACC esterification utilizing the soluble oligomeric coupling reagent OACC. Taken collectively, a total of 208 sultams were successfully generated (89% success rate) with purities >90%. This screening set of sultams represent a diverse motif not currently reported in the literature and has been submitted for biological evaluation via high-throughput screening.

## 4. EXPERIMENTAL PROCEDURES

**General Procedure A for the Synthesis of Library I via a One-Pot Click/aza-Michael Protocol.** To a 1-dram vial containing 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **2** (50 mg, 0.32 mmol, 1 equiv) was added CuI (18.2 mg, 30 mol %), DBU (5 $\mu$L, 10 mol %), dry EtOH (0.64 mL, 0.5 M), amine (0.38 mmol, 1.2 equiv) and azide

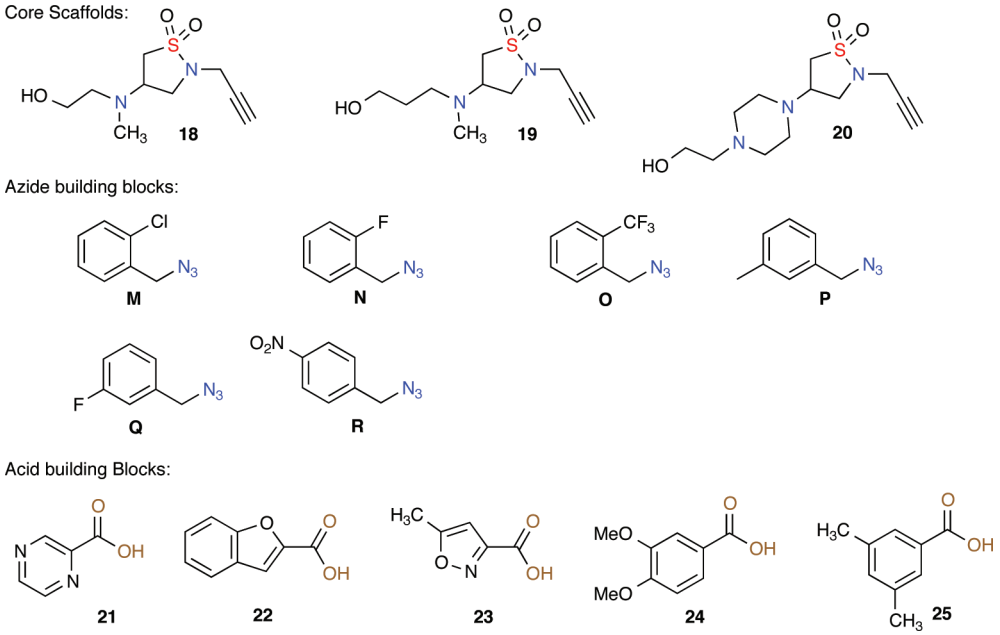
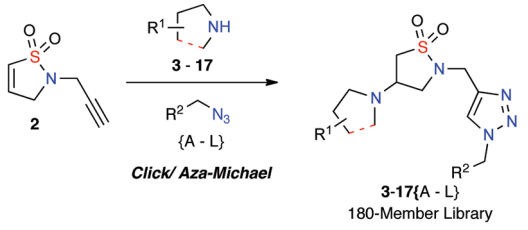
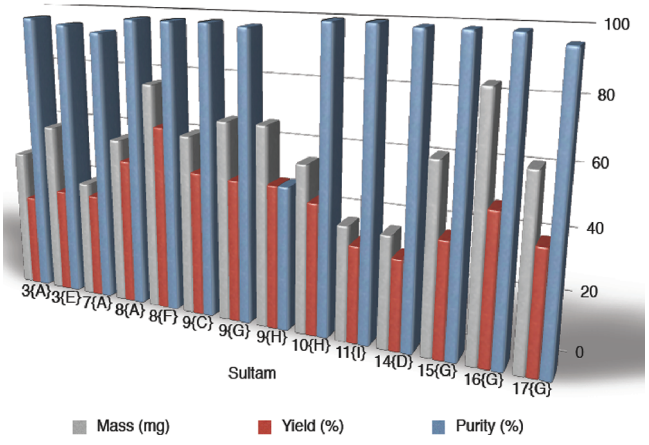



**Figure 4.** Library **C**: Core Scaffolds **18**, **19**, and **20**, azide building blocks **M**−**R** and acid building blocks {21−25}.

### Scheme 2. Library A and B: Representative Library Members Demonstrating Final Mass, Purity, and Overall Yield

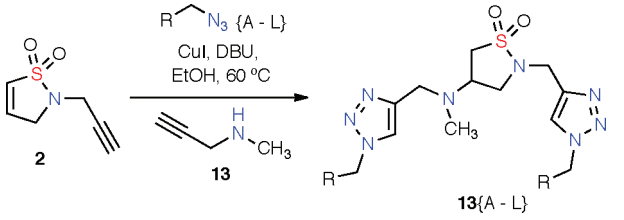


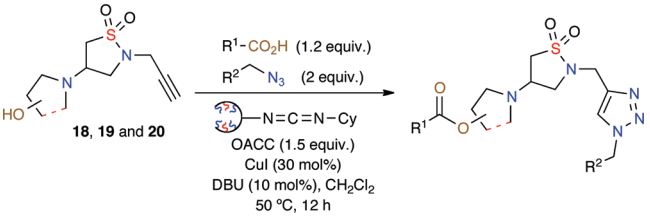

(0.64 mmol, 2 equiv). The reaction was heated at 60 °C on a reaction block for for 12 h, after which time the reactions were cooled, filtered through a $SiO_2$ SPE into preweighed bar-coded vials, washed with eluent (2 mL, EtOAc:MeOH 95:5) and concentrated under reduced pressure. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

***Note**: All reactions involving the use and heating of azides were carried out behind a safety shield taking extra precautions because of the explosive nature of these materials.*

### Scheme 3. One-Pot *bis*-Click/aza-Michael to Produce Compounds 13{A−L}




### Table 3. One-Pot, Click/OACC Esterification




| entry[a] | scaffold | azide | acid | yield (%)[b] |
|---|---|---|---|---|
| 1 | **18** | P | 21 | 48 |
| 2 | **18** | M | 22 | 52 |
| 3 | **18** | M | 23 | 47 |
| 4 | **18** | P | 23 | 60 |
| 5 | **19** | M | 22 | 40 |
| 6 | **19** | M | 23 | 42 |
| 7 | **19** | M | 24 | 43 |

[a] Reaction conditions: Isothiazole 1,1-dioxide (40 mg, 1 equiv), acid (1.2 equiv), azide (2 equiv), OACC (1.5 equiv), CuI (30 mol %), DBU (10 mol %), dry $CH_2Cl_2$ (0.2 M), 50 °C, 12 h. [b] Isolated yields after standard column chromatography (EtOAc, $R_f$ = 0.3−0.6).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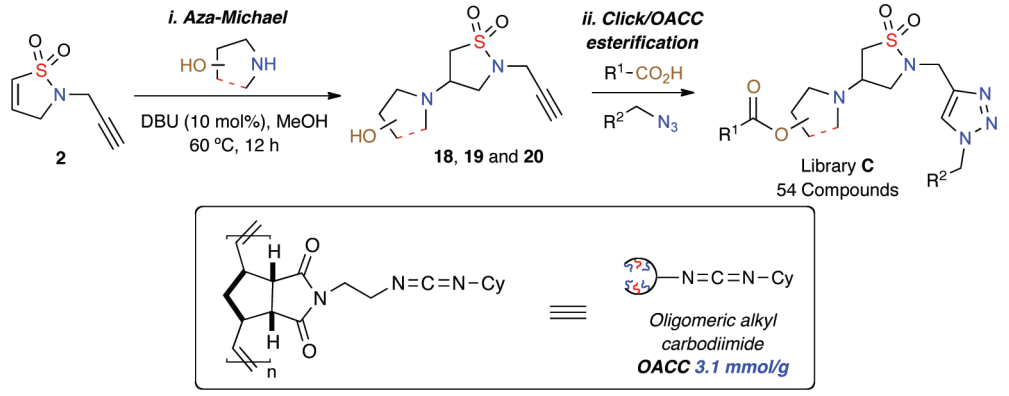
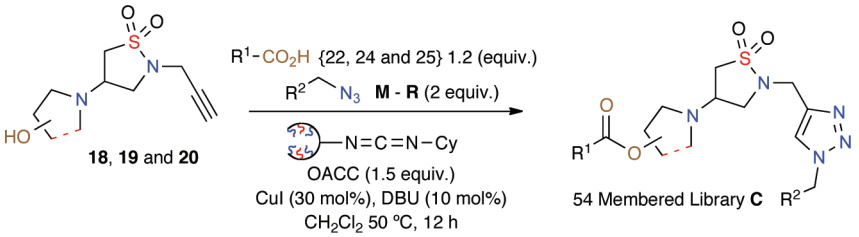
**Scheme 4. Library C; One-Pot, Click/OACC Esterification of Isothiazole 1,1-Dioxides 18, 19, and 20**




**Scheme 5. Generation of Library C via an One-Pot Click/OACC Esterification**




**General Procedure B for Two-Step Click, aza-Michael with Amines 14−17 and Azides A−L.** To a 1-dram vial containing 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **2** (50 mg, 0.32 mmol, 1 equiv) was added CuI (18.2 mg, 30 mol %), DBU (5 $\mu$L, 10 mol %), dry EtOH (0.64 mL, 0.5 M), and azide (0.64 mmol, 2 equiv). The reaction was heated at 60 °C on a reaction block for 4 h, after which time the reactions were cooled, filtered through $SiO_2$, washed with eluent (2 mL, EtOAc), and concentrated under reduced pressure. The crude was transferred to a 1-dram vial, where DBU (5 $\mu$L, 10 mol %), dry EtOH (0.64 mL, 0.5 M), amine (0.38 mmol, 1.2 equiv) were added. The reaction was subsequently heated at 60 °C on a reaction block for 10 h, after which time the reactions were cooled, filtered through a $SiO_2$ SPE and concentrated into preweighed barcoded vials, washed with eluent (2 mL, EtOAc:MeOH 95:5) and concentrated under reduced pressure. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

**General Procedure C for the Synthesis of Cores 18, 19, and 20 via aza-Michael.** Into a round-bottom flask was added a solution of 2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide **2** (1 equiv) in dry MeOH (1 M). To the stirring solution was added DBU (10 mol %) and the corresponding amino alcohol (1.5 equiv), and the reaction mixture was heated at 60 °C for 12 h. After such time, the reaction was diluted in $CH_2Cl_2$/MeOH (9:1), filtered through a silica SPE, and flushed with $CH_2Cl_2$/MeOH (9:1). The resulting isothiazolidine 1,1-dioxide (**18**, **19**, or **20**) was concentrated and carried forward without the need for further purification.

**General Procedure D for Synthesis of Library C via One-Pot Click/OACC Esterification Protocol.** To a 1-dram vial containing sultam **18**, **19**, or **20** (40 mg, 1 equiv) was added CuI (30 mol %), DBU (10 mol %), dry $CH_2Cl_2$ (0.2 M), acid (1.2 equiv), and azide (2 equiv). To the crude mixture was added a solution of OACC (1.5 equiv) in dry $CH_2Cl_2$ (0.2 M), and the resulting reaction mixture was heated at 50 °C on a reaction block for 12 h. After which time, the reactions were cooled, diluted in EtOAc (2 mL), and the corresponding suspension filtered through a $SiO_2$ SPE into preweighed bar-coded vials, washed with eluent (2 mL, EtOAc) and concentrated under reduced pressure. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures, tabulated results for all libraries, and full characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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