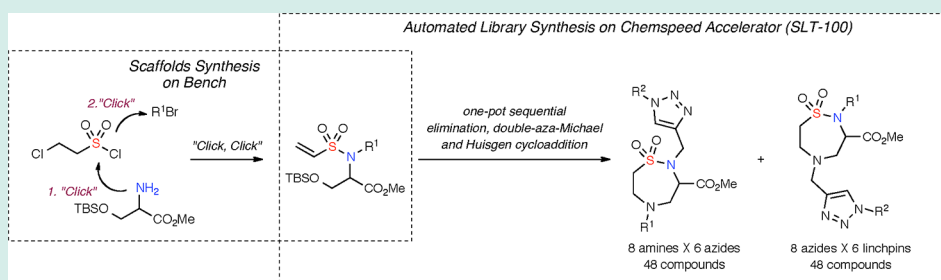# Automated Synthesis of a Library of Triazolated 1,2,5-Thiadiazepane 1,1-Dioxides via a Double Aza-Michael Strategy

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Ⓢ *Supporting Information*

ABSTRACT: The construction of a 96-member library of triazolated 1,2,5-thiadiazepane 1,1-dioxides was performed on a Chemspeed Accelerator (SLT-100) automated parallel synthesis platform, culminating in the successful preparation of 94 out of 96 possible products. The key step, a one-pot, sequential elimination, double-aza-Michael reaction, and [3 + 2] Huisgen cycloaddition pathway has been automated and utilized in the production of two sets of triazolated sultam products.

KEYWORDS: aza-Michael, triazolated 1,2,5-thiadiazepane 1,1-dioxides, parallel synthesis

Automated synthesis, in which robots and machines carry out much of the bench work, including setting up reactions, workup, purification, and analysis, has emerged as the consequence of the growing demand of hit discovery for the development of therapeutic agents.[1,2] Historically, automated synthesis has found heavy use in the area of peptide synthesis,[3] polymer synthesis,[4] and carbohydrate synthesis.[5] Takahashi and co-workers utilized an automated synthesizer in a 36-step formal total synthesis of Taxol.[6] The examples of automated synthesis of complex natural products are further enriched by the synthesis of grossamide[7] and oxomaritidine[8] from Ley and co-workers, as well 9-membered masked enediynes[9] and spiruchostatin B[10] from the Takahashi group.

Previously, an inter/intramolecular double aza-Michael pathway was employed as the cyclization step using tertiary sulfonamides containing TBS-protected serinol methyl ester moiety (Scheme 1).[11] Automation and scale out of the inter/intramolecular double aza-Michael addition using a microwave-assisted, continuous flow organic synthesis platform (MACOS) further optimized this "Click, Click, Cy-Click" process.[12] As an alternative approach, and as part of a larger program aimed at the facile production of sulfur-[13,14] and phosphorus-containing heterocyclic libraries for early phase drug discovery, we herein report the synthesis of a 96-member library of triazolated 1,2,5-

Scheme 1. Previously Reported Click, Click, Cy-Click Process
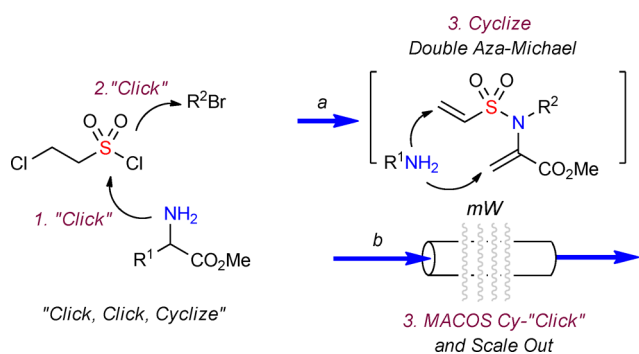
thiadiazepane 1,1-dioxides using a Chemspeed Accelerator (SLT-100) automated parallel synthesis platform for facile production of the titled compounds.

Chemical Method. The vinylsulfonamide linchpin **3** was prepared via sulfonylation of TBS-protected serinol methyl
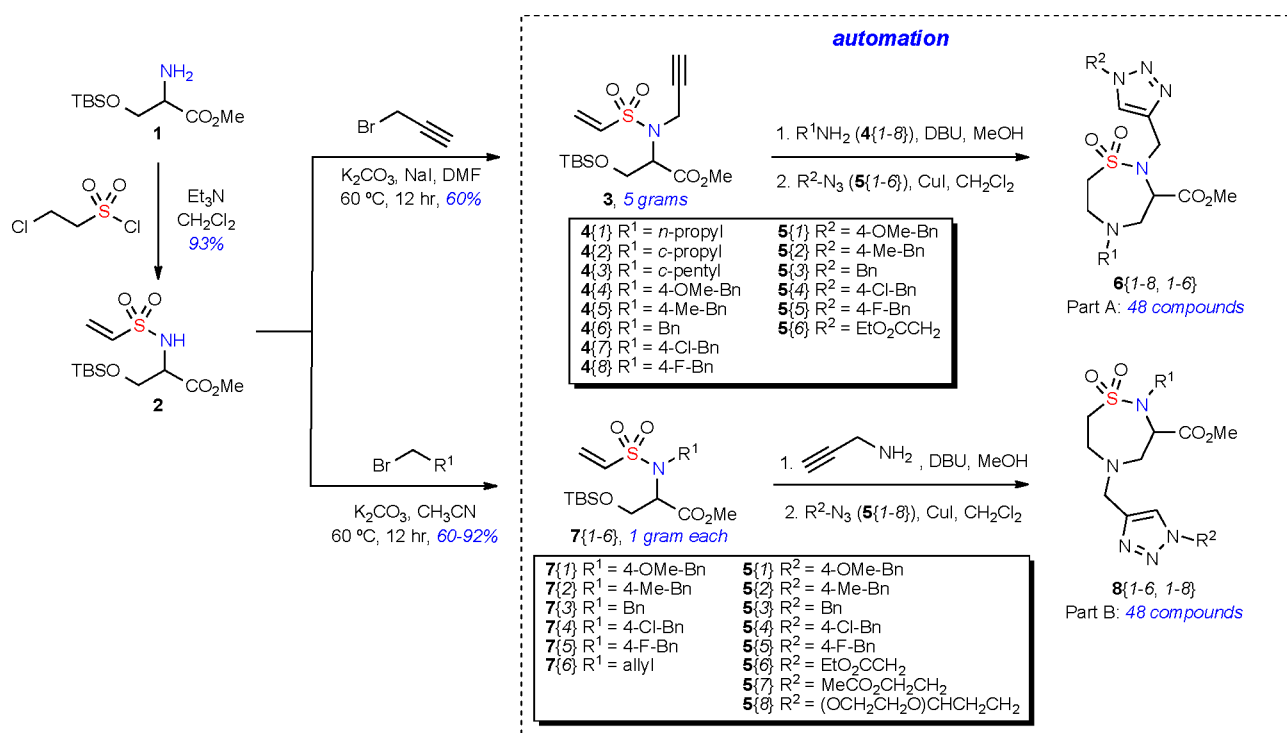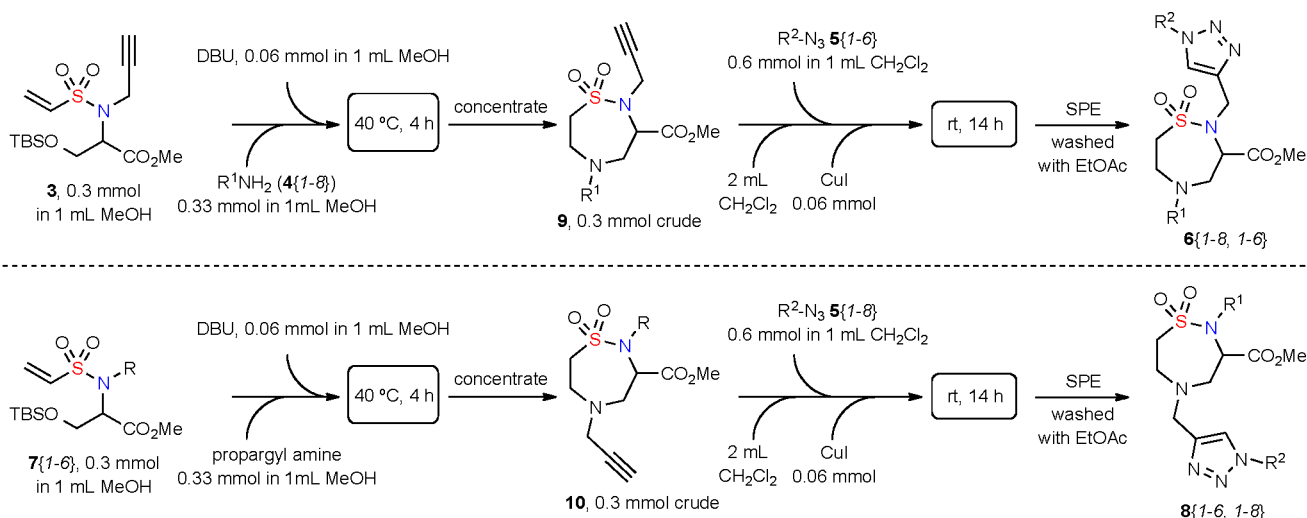
Scheme 2. Utilizing a One-Pot, Sequential Elimination, Double-Aza-Michael Reaction, and [3 + 2] Huisgen Cycloaddition in the Synthesis of Triazolated 1,2,5-Thiadiazepane 1,1-Dioxides

Scheme 3. Automation of a One-Pot, Sequential Elimination, Double Aza-Michael and Huisgen Cycloaddition Step


ester (**1**), followed by sulfonamide alkylation. This scaffold was prepared on 5-g scale with a yield of 56% over three steps. A sequential one-pot elimination, double aza-Michael addition of eight amines **4**{*1–8*}, and subsequent [3 + 2] Huisgen cycloaddition with six azides **5**{*1–6*} generated the 48-member library of **6**{*1–8, 1–6*} (Part A, Scheme 2). Likewise, vinylsulfonamide linchpins **7**{*1–6*} were prepared in good yield and on 1-g scale. The orientation of triazole groups were "flipped" in producing another set of 48 compounds [**8**{*1–6, 1–8*}, Part B] merely by switching to propargyl amine which serves as both the double aza-Michael reaction donor and cycloaddition partner with eight azides **5**{*1–8*}.

Library Design. For selecting building blocks, physico-chemical property filters were applied, guiding the elimination

of undesirable building blocks that led to products with undesirable in-silico properties.[15] These metric filters included standard Lipinski Rule of 5 parameters[16] (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[17] along with diversity analysis using standard H-aware 3D BCUT descriptors[18] comparing against the MLSMR screening set (ca. 7/2010; ~330,000 unique chemical structures).

Automated Library Synthesis. The automated one-pot, sequential elimination, double aza-Michael and Huisgen cycloaddition was performed on a Chemspeed Accelerator

Chart 1. Library: Final Mass, Purity, and Yield

Final Mass

Final Purities

Final Yields
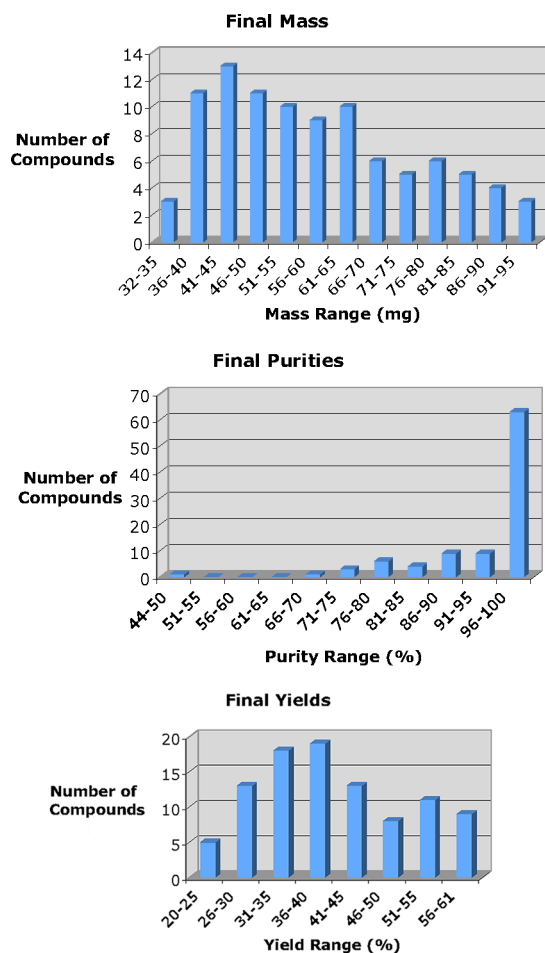
(SLT-100) automated parallel synthesis platform. For the synthesis of **6**{*1–8, 1–6*}, 1 mL of 0.3 M stock solution of linchpin **3** in MeOH was distributed to each of 48 reactors. One mL of 0.06 M stock solution of DBU in MeOH was then added to each reactor, followed by the addition of 1 mL MeOH solution of 0.33 mmol amines **4**{*1–8*}. The reaction mixture was heated at 40 °C for 4 h, after which the solvent was removed under reduced pressure. To the crude products of **9**, 2 mL of CH_2Cl_2 was charged into each reaction vessel, followed by 0.6 mmol of azide **5**{*1–6*} in 1 mL CH_2Cl_2. Solid CuI (0.06 mmol) was dispensed into reaction vessels and the reactions were stirred overnight at room temperature. The mixtures were then allowed to pass through SPE, flushed with EtOAc, and the crude products of **6** were collected in bar-coded, preweighted vials. Compounds **8**{*1–6, 1–8*} were prepared in a similar process, in which six stock solutions of linchpin **7** was used as Michael acceptor, and propargyl amine for the double-aza-Michael donor (Scheme 3).

Result Analysis. The crude products collected in bar-coded, preweighted vials were concentrated in reduced pressure and subjected to preparative/mass-directed HPLC purification. The key to successful library production was to obtain compounds in >90% purity in 40−50 mg quantities, which would be sufficient for HTS screening via the Molecular Library Probe Center Network (MLPCN) (20 mg), external biological outreach screening partners (20 mg), and to retain a sample (10 mg) for follow-up evaluation or to resupply the MLPCN. Final assessment of part A and B demonstrated that these

primary objectives set out in the library design were achieved; final average mass was obtained as 58 mg with average purity as 94%, and the average yield was 40% (Chart 1). A total of 94 products from the proposed 96-membered library met the requirements and have been submitted to MLPCN and other screening partners.

In conclusion, the automated production of a library of 94/96-member triazolated 1,2,5-thiadiazepane 1,1-dioxides has been successfully completed. All the procedures of liquid and solid transferring, reaction stirring and heating, solvent evaporation, and solid phase extraction (SPE) were automatically carried out with "no human intervention", except for software setup and stock solution preparation. The products have been submitted for evaluation of their biological activity in high-throughput screening assays at the NIH MLPCN and the results will be reported in due course.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, tabulated results and data for this library, as well as full characterization for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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