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One-Pot Synthesis of Thio-Augmented Sulfonylureas via a Modified Bunte's Reaction

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Cite This: *ACS Omega* 2022, 7, 31612−31620

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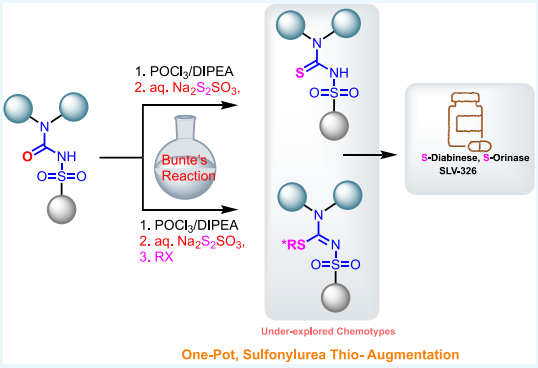
ABSTRACT: We report the development of a one-pot Bunte's reaction-enabled expeditious platform under aqueous conditions for the scalable conversion of sulfonylureas to synthetically versatile thio-sulfonylureas. The reaction was further propagated in the same pot to yield diverse chiral and achiral isothiosulfonyl analogs. The protocol enabled the synthesis of various drug-like molecules and was applied to an enantiomeric synthesis of a cannabinoid receptor antagonist SLV326.



INTRODUCTION

Chalcogenide elements of the periodic table, namely, sulfur in its various oxidation states are proving to be indispensable in modern medicinal and environmental applications.[1,2] Interrogating biological problems and treating complex diseases require new approaches to the generation of novel chemical probes and drug-like molecules often in scalable quantities. Synthetic innovation can steer the exploration of new chemical space around under-utilized scaffolds to expand their potential further in biochemical applications. In this regard, a class of ureas—sulfonylureas (SUs)—have long been used as antidiabetic agents and impact a range of biological pathways.[3−6] They are reported to have anti-aging properties[7] and are proposed as an auxiliary therapy for Alzheimer's disease.[8] They have a role in ameliorating inflammatory pathways by acting as inflammasome inhibitors.[9,10] They can also act as potassium ATP channel modulators[11] and ACAT inhibitors.[12] (Figure 1A).[9] They are also used widely as herbicides,[13] antihelminthics,[14] and acaricides.[15−17] Antimicrobial and fungicidal activities are also attributed to sulfonylurea compounds.[18] Sulfonylthioureas (STUs) are also purported to have insecticidal activities[19] and anticonvulsant properties.[20]

Synthetic routes to obtain sulfonylureas have been reviewed recently.[21] As for STUs, many applications explore a limited number of these analogs, possibly due to the lack of robust routes to generate them.[22,23] Thiourea analogs have important utility in the synthesis of therapeutically important guanidine compounds in the presence of $HgCl_2$.[24] Generation of STUs would also enable the synthesis of isothiourea derivatives, which can have novel properties and applications.[25−27] An additional innovation would be to generate novel, nontraditional chemotypes with S-bearing stereocenters, which are one of the underexplored pharmacophores in the biological realm (Figure 1A).[28]

In this report, we highlight a simple, one-pot sequential approach to generate terminal sulfonyl thiocarbamide analogs or its propagation to obtain sulfonylisothiocarbamide analogs in a complex scaffold. The utility of the protocol was further demonstrated in a supercritical chromatography (SFC)-free assembly of an enantiomeric active pharmaceutical ingredient (API).

Current methods to convert urea to thiourea-containing derivatives involve the use of volatile and flammable carbon disulfide and toxic and corrosive thiophosgene and malodourous reagents like Lawesson's reagents, P_2S_5, NaHS, and H_2S at high refluxing temperatures.[29−31] A commonly used process for the synthesis of thioureas involves unstable isothiocyanates (Figure 1D).[32] These routes however remain mercurial for the generation of chalcogenide analogs of SU. A recent approach showed that aryl sulfonylisoureas and isothioureas can be generated from the alcohol/thiol source using dibromoarylsulfonamides and isocyanides.[33] Thus, a practical and environment-friendly process for sulfonyl thiocarbamide construction in complex molecular scaffolds is highly desirable but still remains a challenge in organic synthesis.

Received: July 29, 2022
Accepted: August 10, 2022
Published: August 23, 2022

https://doi.org/10.1021/acsomega.2c04816
ACS Omega 2022, 7, 31612−31620

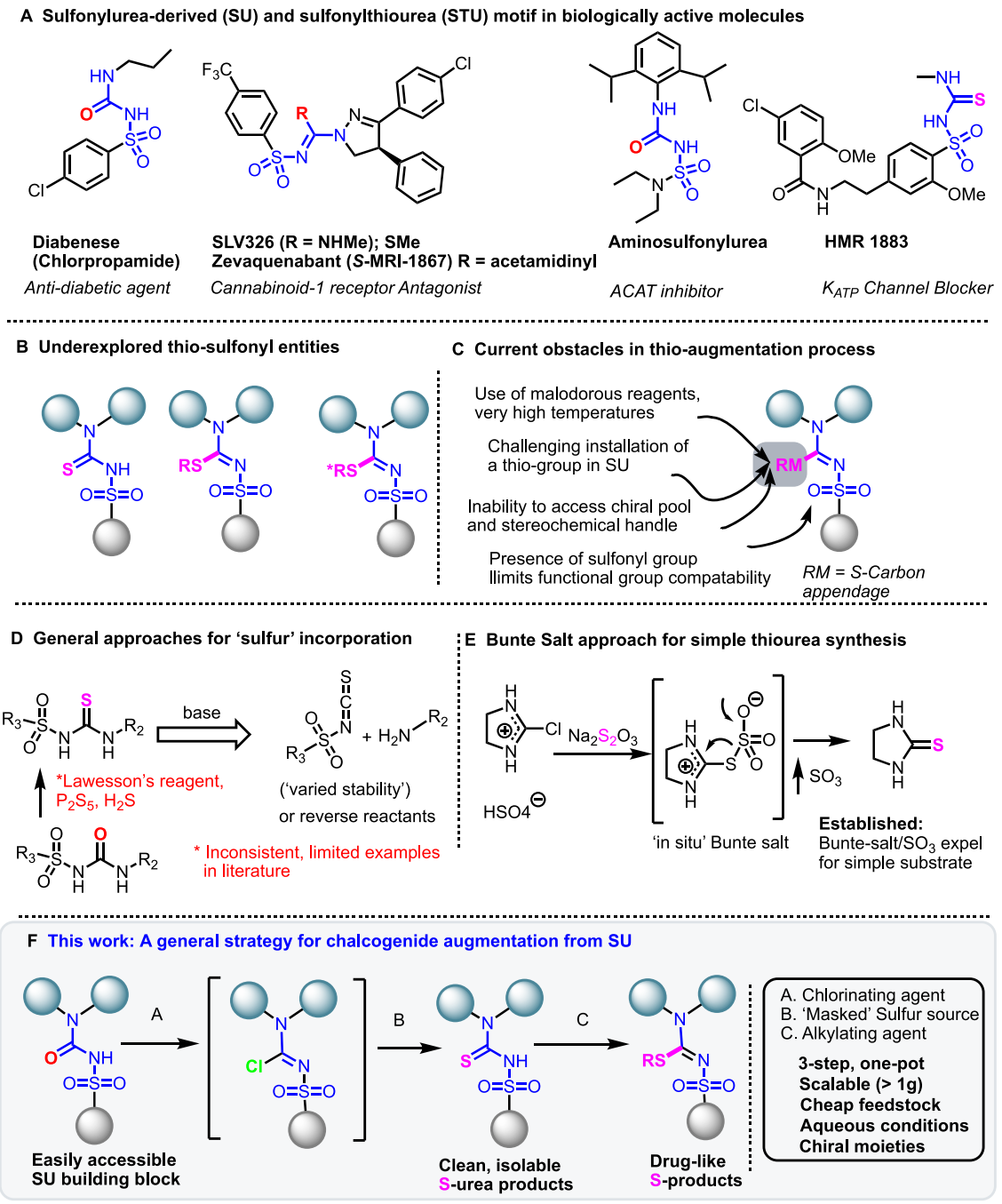


Figure 1. Background of sulfonylurea motifs and chalcogenide sulfonylurea synthesis.

Organic thiosulfates ($RSSO_3M$, M = Na, K) are commonly known as Bunte salts named after Hans Bunte, who first reported them in 1874.[34,35] They are known for their ability to be used as "sulfur surrogates."[36] A direct synthesis of thiols from halo-heterocycles using sodium thiosulfate has been reported by Foye and co-workers.[37] Recently, 2-chloro-4,5-dihydroimidazole hemisulfate was subjected to a reaction with sodium thiosulfate in aqueous solution at room temperature.[38] An exothermic nucleophilic substitution reaction forming the internal Bunte salt, followed by a vigorous evolution of SO_3, gave imidazolidine-2-thione in good yields (Figure 1E).[38] Many methodologies have appeared expanding the use of Bunte salts.[36] Despite the well-established application of SUs in various biological and environmental settings, there is a paucity of routes for STU and sulfonylisothiourea (SITU) generation. We questioned whether we could integrate Bunte salt to an SU motif to selectively deliver STU, which could also be propagated to generate SITU analogs for diverse applications. On this basis, we hypothesized that a sulfonylurea imidoylhalide may serve as an intermediate precursor to sulfonylurea Bunte salt under right conditions, which may then collapse to yield isolable STUs. This pathway, if successful, would generate sulfonyl-bearing chalcogenide adducts with myriad provisions for amino inclusions/alterations. A protocol that allows for the generation of chalcogenide analogs based on SUs and concurrent augmentation to a chiral and prochiral handle will be a formidable platform for diversity-oriented synthesis (Figure 1F).

https://doi.org/10.1021/acsomega.2c04816
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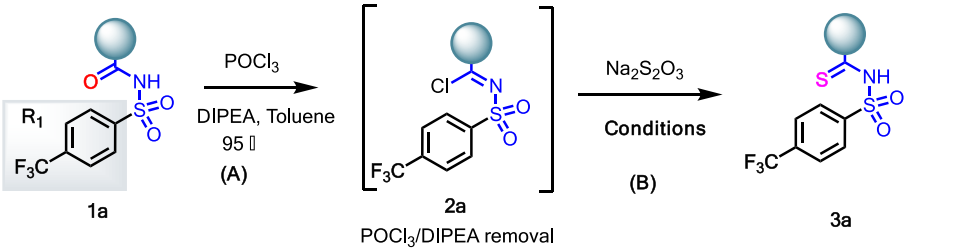
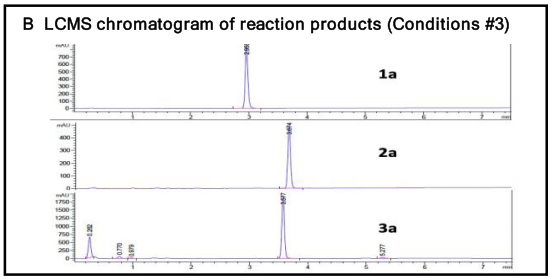
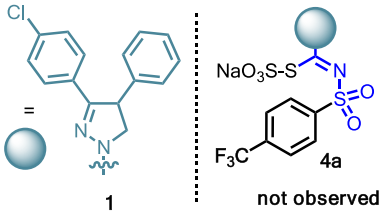
Table 1. Screening of Reaction Conditions Using 1a (100 mg Scale/1 mmol Scale)[f]

A Streamlined process for sulfonylthiourea synthesis using 1a as model system[a]



B LCMS chromatogram of reaction products (Conditions #3)





C optimization conditions[a]

entry	reagent/equiv	solvent[b]	temp (°C)	time to complete conversion[c]/% yield from **1a**[d,e]
1.	$Na_2S_2O_3$ (5 equiv)	MeOH−H_2O	RT	12/[c]85%
2.	$Na_2S_2O_3$ (5 equiv)	MeOH−H_2O	55	2 h/[c]80%
3.	$Na_2S_2O_3$ (2 equiv)	MeOH−H_2O	90	20 min/[d]91%
4.	$Na_2S_2O_3$ (5 equiv)	MeOH	55	3 h/[c]70%
5.	$Na_2S_2O_3$ (2 equiv)	MeOH	85	1 h/[c]84%
6.	$Na_2S_2O_3$ (2 equiv)	EtOH−H_2O	90	20 min/[c]NA
7.	$Na_2S_2O_3$, (2 equiv)	dioxane−H_2O	85	30 min/[d]72%
8.	$Na_2S_2O_3$, (2 equiv)	toluene−H_2O	90	-/traces
9.	$Na_2S_2O_3$, (2 equiv)	DMF−H_2O	85	30 min/[d]68%
10.	$Na_2S_2O_3$, (2 equiv)	acetonitrile−H_2O	85	1 h/[c]68%

[a]Reaction conditions: **1a** (0.2 mmol scale/see the Supporting Information, SI, for additional details). [b]Water was used at a maximum of 10% solvent combination. [c]Conversion based on liquid chromatography−mass spectrometry (LCMS) comparison with intermediate imidoylchloride **2a**. [d]Yield based on work-up/MeOH-IPA (1:1) trituration. [e]Yield based on work-up/flash chromatography (40% hex/EtOAc). [f][A] Streamlined process for sulfonyl thiourea synthesis. [B] Reaction monitoring of crude thiourea. [C] Optimization of reaction conditions.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. FDA approved drugs like chlorpropamide and tolbutamide, which are sulfonylureas that are commercially available and could support feasibility studies. 3,4-Diarylpyrazoline sulfonylureas and thioureas are purported to have insecticidal activity.[19] They also serve as precursors to potent cannabinoid-1 (CB1) receptor blockers, which are currently being explored for ameliorating a range of health conditions.[39] Hence, we were tempted to initially explore the generation of 3,4-diarylpyrazoline sulfonylthioureas directly from the sulfonylurea intermediate precursors.[40−43] Additionally, a robust way of generating sulfonylthioureas would help practicing chemists to assay the properties of SU and STU in parallel. In an optimized approach, we now show the successful execution of the reaction depicted in Table 1. We present a protocol, where an inexpensive, odor-free and safe inorganic thiosulfate can displace an SU imidoylchloride to deliver clean, isolable sulfonyl-containing thioureas. Using **1a** as the model system, imidoylchloride **2a** could be obtained cleanly from substrate **1a** by treatment with $POCl_3$/*N*,*N*-diisopropylethylamine (DIPEA) at 90 °C. Upon subsequent treatment with $Na_2S_2O_3$ ($0.05/g), the putative formation of a Bunte intermediate (not detected) led to the generation of carbothioamide analogs in excellent yield (Table 1C).

This one-pot, two-step protocol with or without the isolation of the intermediate imidoylchloride bypasses the need for sensitive isothiocyanate precursors. The imidoylchloride intermediate could also be generated from PCl_5 in refluxing chlorobenzene although decomposition side products were seen alongside (SI). The nucleophilic displacement of imidoylchloride **2a** by the thiosulfate ion worked best in methanol/H_2O at 90 °C, and the thiourea analog could be generated within 20 min. The nucleophilic displacement also worked well in methanol/H_2O at 55 °C with excess (5 equiv) $Na_2S_2O_3$ over a period of 2 h. The reaction worked sluggishly at room temperature and proceeded to give **3a** over extended reaction times (~12 h). Dimethylformamide (DMF)/H_2O, ethanol/H_2O, and acetonitrile/water were acceptable solvents for the reaction. The reaction also proceeded in aqueous dioxane although somewhat slower, and only traces of the product could be obtained in aqueous toluene. Water was deemed essential for solubilization of the inorganic reactant, albeit the reaction did proceed in alcoholic solvents likely due to adventitious water. In general, we observed that with substrate **1a**, the reaction had a

https://doi.org/10.1021/acsomega.2c04816
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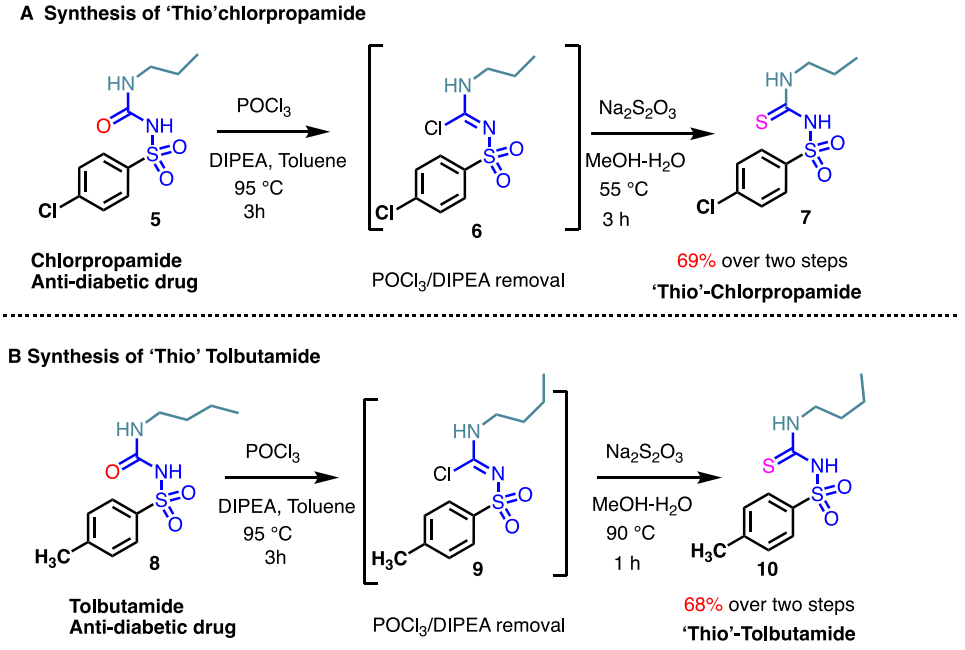
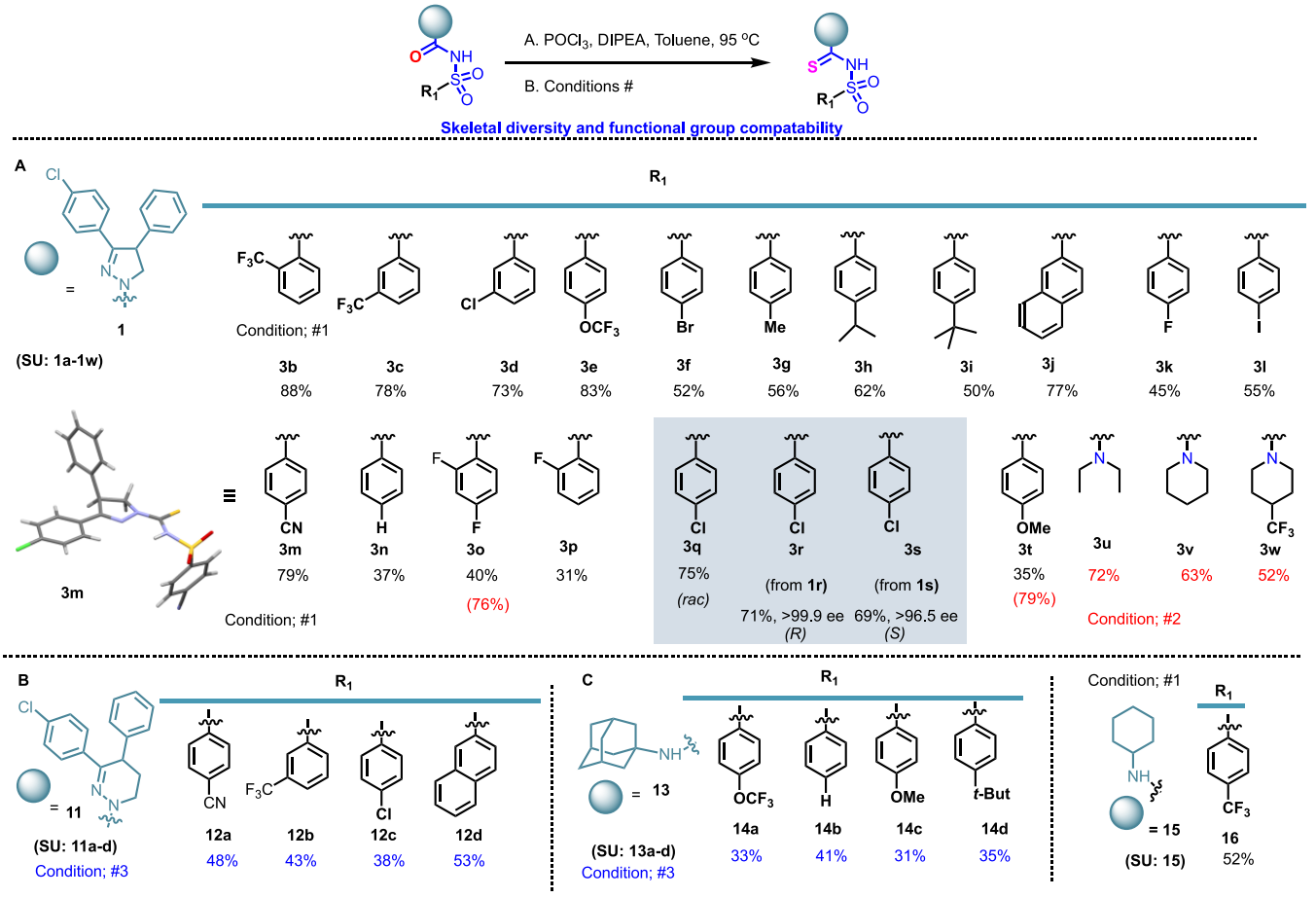
Scheme 1. Thio-Antidiabetic FDA-Approved Drugs Synthesized through the Present Protocol [A] and Thio-Chlorpropamide (Diabinese) (1 g Scale) and [B] Thio-Tolbutamide Synthesis (Orinase) (1 g Scale)



Scheme 2. Scope and Skeletal Diversity for the Bunte Reaction of Sulfonylureas (See the Yield Color Code for Conditions#)



large range of temperature flexibility, where the STU product **3a** could be obtained without significant loss of yield.

With the optimized protocol in hand, we tested whether the antidiabetic drugs chlorpropamide and tolbutamide would

https://doi.org/10.1021/acsomega.2c04816
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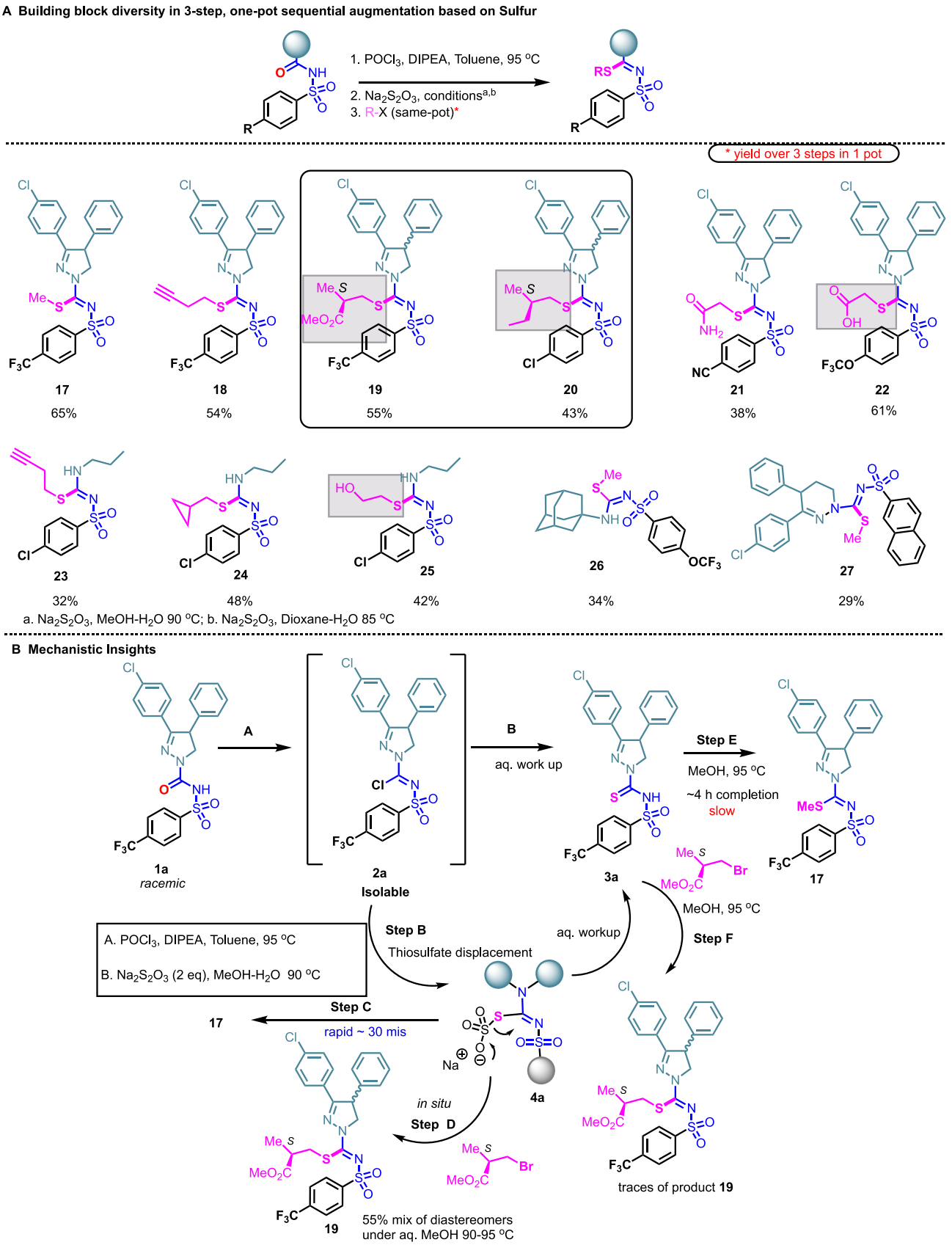
Scheme 3. Modification to Diverse Thiosulfonyl Functionality [A] Building Block Diversity for Three-Step, One-Pot Chalcogenide Sulfonylurea Functional Group Propagation and [B] Mechanistic Insights in Three-Step, One-Pot Thiosulfonyl Augmentation



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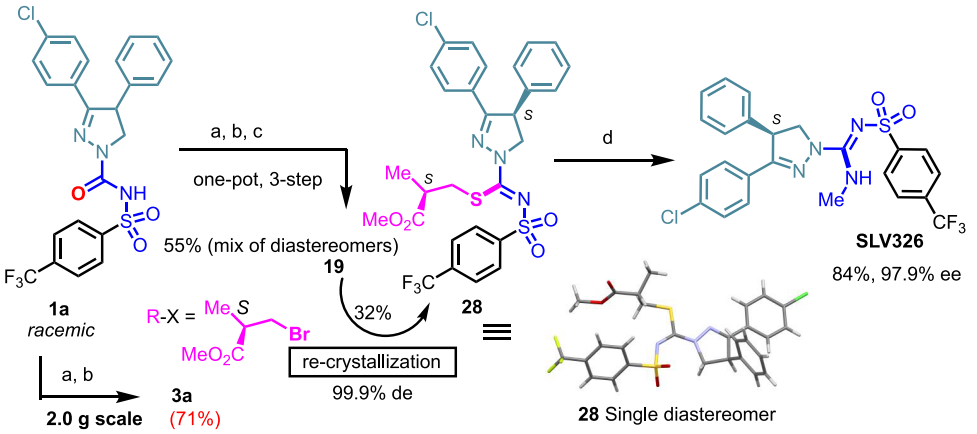
Scheme 4. Gram-Scale Synthesis and Application of the Protocol in Chiral Synthesis of Cannabinoid-1 Receptor Antagonists



[a] $POCl_3$, DIPEA, Toluene, 95 °C [b] $Na_2S_2O_3$, MeOH-H_2O, 90 °C [c] R-X, 95 °C
[d] Methylamine, CH_2Cl_2-MeOH, Et_3N

undergo the oxo-edits. Indeed, on a gram-scale, both compounds underwent the imidolylchloride conversion and the subsequent thiosulfate displacement, leading to clean corresponding thiourea products in yields greater than 65% (Scheme 1).

SUBSTRATE SCOPE

Having ready access to a range of 3,4-diarylpyrazoline SU products, we then proceeded to test the scope of conversion of 3,4-dihydropyrazoline sulfonylurea precursors to substituents that could be tolerated on the arylsulfonyl part of the molecule. To our delight, many of the commonly used groups for structure−activity relationship (SAR) studies in biological applications (**1a−t**) were very well tolerated under the optimized reaction conditions. As seen in Scheme 2, a wide variety of substituted sulfonylurea precursors[40] proceeded to provide the STU in good to excellent yields. 3,4-Dihydropyrazoline compounds of type **1**/**3** bear a stereocenter at the C4 pyrazoline ring.

Therefore, in the case of example **1q** (4-chlorophenyl substituent), we used the racemic *R* as well as *S*-enantiomer of the SU precursor to generate the corresponding thiourea products. Gratifyingly, we saw that the two-step, one-pot protocol proceeded to give the thio-products with no erosion of chirality as documented by chiral high-performance liquid chromatography (HPLC) (SI). Replacement of the aryl groups at the sulfonyl end with dialkyl or cyclic amino pendants in the 3,4-diarylpyrazoline SU precursors (**1u−w**) also provided the sulfonylthioureas (**3u−w**) in yields above 50%. Conditions 2 in Table 1C were deemed to be optimal for substrates **1u−w**. We also observed that yields of the products were largely unaffected by the electronics on the sulfonyl end of the molecule.

We then proceeded to test the scope of the substituents at the nonsulfonyl end of the molecule. Various amino precursors could be utilized at this end of the molecule. Replacement of the pyrazoline core with pyridazinyl attachment also led to the conversion of urea to thiourea sulfonyl moieties (Scheme 2). Subtle differences in temperature to affect the thiosulfate displacement and use of aqueous dioxane in lieu of methanol were required to obtain the thiourea products (**12a−d**). Additionally, substituents like a dense adamantyl group and simple rings were also well tolerated as seen in examples **13a−d**, **15**.

MODIFICATION APPROACHES

To maximize the utility of this new protocol, we posited that the Bunte salts can be alkylated "*in situ*" to generate sulfonylisothiourea analogs. Treatment of **3a** reaction mixture containing the preformed "masked STU" underwent facile alkylation in the same pot upon reaction with methyl iodide, resulting in a clean conversion to the S-methylated analog **17** (Scheme 3). This analog has potent cannabinoid-1 receptor antagonist activity.[40] It should be noted that the reaction required a slight excess of the alkylating precursor for complete transformation. A clear hint that the reaction occurs on the putative Bunte salt **4a** with concomitant alkylation along with SO_3 extrusion was seen with faster reaction times of the *in situ* alkylation as opposed to the alkylation in methanol after thiourea isolation (Scheme 3A,B).

That this reaction could proceed smoothly under wet alcoholic conditions gave us hope that other alkylation agents/STU may also be amenable to this transformation, yielding novel isothiosulfonyl molecular scaffolds. Importantly, we were able to utilize unprotected alkylating precursors like butynyl bromide (**18**/**23**) bromo-acetic acid and bromoethanol to yield chemotypes **22** and **25**, respectively, on different STU scaffolds, which could be primed for downstream coupling manipulations. It became clear to us that we could also use chiral alkylating agents to drive this synthesis toward stereoselective products. Expanding on those lines, the strategy was successfully executed by the reaction of racemic **1a** with methyl (*S*)-3-bromo-2-methylpropanoate to uneventfully yield **19** as a diastereomeric mixture. Similarly, racemic **1q** could be turned into a diastereomeric mixture **20** using a chiral alkylating agent ((*S*)-1-bromo-2-methylbutane). As seen in Scheme 3B, for the alkylation procedure, in situ trapping of Bunte salt without thiourea isolation (step C/D) is the method of choice. The alkylation of thiourea of type **3a** proceeds to give products in good yields even under aqueous methanol or dioxane. When the thiourea was isolated and alkylation attempted in methanol/95 °C (step E/F), the reaction proceeded sluggishly (MeI) or small traces of products were seen in the case of alkylating agents like (*S*)-3-bromo-2-methylpropanoate.

https://doi.org/10.1021/acsomega.2c04816
ACS Omega 2022, 7, 31612−31620

With the wealth of combinations available as building blocks for amino, sulfonyl, and alkylating agents, one could envision constructing a diverse screening library based on this synthetic platform.

Also, this protocol would open avenues for the generation of novel thio-mimics and warheads.

Finally, we sought to exploit this methodology in the preparation of substituted 4,5-dihydro-1*H*-pyrazoles that are useful as potent cannabinoid receptor antagonists. Recently, we and others have employed such scaffolds to generate novel, selective agents that have the potential in treating fibrosis, obesity, and related metabolic disorders.[39−41,44−46] Thus, there remains a need for an efficient, high-yielding, and scalable synthetic approach to provide substantial amounts of enantiomerically pure active pharmaceutical ingredients (APIs) in the chiral pyrazoline series for biological evaluation. As a proof of principle, our current protocol provided validation of its orthogonal utility by enabling an expeditious assembly of a chiral pyrazoline sulfonyl carboximdamide CB_1 receptor antagonist, SLV326.[47] We decided to apply our newly developed protocol by utilizing an isothiourea-based chiral auxiliary/decoy intermediate to generate diastereomeric isothiourea precursors, which could be displaced by an amino pendant to give a chiral supercritical chromatography (SFC)-free approach to generate enantiomeric APIs.

Compounds of type **1a** have a singular quaternary carbon stereocenter at the C4 position of the pyrazoline ring. Previous methods have used chiral HPLC/SFC separation of the final racemic mixture to yield the biologically active *S*-enantiomer.[40,41] Since our methodology was amenable to multigram-scale synthesis of STU precursor **3a** (71% yield on a standalone 2.0 g scale), we chose to synthesize the precursor of type **28** (via **19**) through an in situ chiral alkylating agent bearing a known stereocenter. This ensured access to a separable diastereomeric mixture, which could afford a single diastereomer of type **28**. Displacement of the thioalkyl group under controlled basic conditions can then deliver the requisite enantiomeric API (Scheme 4). The diastereomeric mixture **19** thus enabled the generation of single diastereomer **28** through preferential recrystallization. Chiral HPLC analysis showed that the crystals were indeed enriched in one of the diastereomeric forms (*S*,*S*). The stereochemistry of the diastereomer was assigned by separation on *R*,*R*-Whelk-O chiral column and X-ray crystallography (SI). Knowing the stereochemistry at the *S*-alkylation center, the *S*,*S*-diastereomer was treated individually with methyl amine in a DCM:MeOH/Et_3N mixture to obtain SLV326. Isolation of SLV326 and comparison of literature data showed that the transformation proceeded with 97.9% ee and in 84% yield for the final step.

CONCLUSIONS

In summary, we have successfully achieved a facile protocol for oxo-edits based on a modified Bunte salt approach in sulfonylurea molecules to the sulfur atom. The reaction relies on a sequential one-pot generation of an imidoylchloride, followed by a putative Bunte salt formation, which expels sulfur trioxide to create a new C−S bond. Additionally, common sulfonyl thiourea intermediates could be alkylated in the same pot to various sulfur pendant side chains. We have demonstrated a high sulfonylurea substrate tolerance of this method and its application to diverse chiral and achiral *de novo* sulfur-containing drug-like molecules. A further validation of this protocol was achieved by a successful application of this strategy in a high-yield synthesis of potent dihydropyrazoline class of cannabinoid antagonists, enabled by a key diastereomeric intermediate bearing a chiral isothiourea handle. An added advantage of this protocol is the use of cheap feedstock (inorganic thiosulfate) under aqueous conditions with clean, isolable products under controlled temperatures and solvents employed. The robust and expedient reaction conditions along with adaptable precursors in this transformation will help expand the underexplored chemical space of isothio-based (chiral) analogs and provide downstream access to expanding S-oxidation states or utilizing them as decoy substrates for synthetic transformation. We reckon that this protocol will serve as a versatile tool in many milieus and will help influence the assembly of diverse target libraries based on thio-sulfonylurea entities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04816.

Supporting information ^1H NMR, $^{13}C\{^1H\}$ NMR, HPLC traces, chiral HPLC traces, and related data (PDF)

Crystallographic data **3m** (CIF)

Crystallographic data **28** (CIF)

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Notes

The authors declare the following competing financial interest(s): The United States of America as represented by the Secretary, Department of Health and Human Services has filed provisional patent applications on compounds and the subject matter related to this study.

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ACS Omega 2022, 7, 31612−31620

■ ACKNOWLEDGMENTS

This work was supported by intramural funds from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to M.R.I. The authors thank Dr. George Kunos for reading the manuscript and helpful suggestions. For help with HRMS data, John Lloyd is acknowledged. Dr. Klaus Gawrisch and Dr. Walter Teague are acknowledged for their help with NMR experiments.

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