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One-Pot Parallel Synthesis of Alkyl Sulfides, Sulfoxides, and Sulfones

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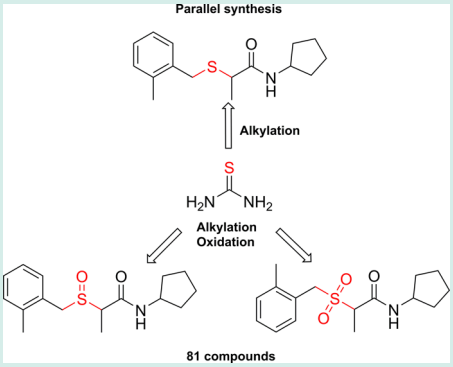
Supporting Information

ABSTRACT: A simple and cost-effective one-pot parallel synthesis approach to sulfides, sulfoxides, and sulfones from thiourea was elaborated. The method combines two procedures optimized to the parallel synthesis conditions: alkylation of thiourea with alkyl chlorides and mono or full oxidation of in situ generated sulfides with H_2O_2 or H_2O_2–$(NH_4)_2MoO_4$. The experimental set up required commonly used lab equipment: conventional oven and ultrasonic bath; the work up includes filtration or extraction with chloroform. The method was evaluated on an 81 member library of drug-like sulfides, sulfoxides, and sulfones yielding the compounds on a 30−300 mg scale. A small-scale synthesis of 2-(benzhydrylsulfinyl)acetamide (modafinil) utilizing our approach resulted in similar efficiency to the published procedures.



KEYWORDS: *one-pot parallel synthesis, alkylation of thiourea, alkyl chlorides, oxidation of alkyl sulfides, ammonium molybdate*

INTRODUCTION

A frequently applied synthetic approach to drug-like compounds for high-throughput screening (HTS) involves a covalent linking of two small functionalized fragments (building blocks). The linking is performed either directly or with a linker. The selection of the linker relies on: (1) small size, (2) minimal number of rotating bonds, and (3) reliable synthetic method that generates large set of compounds.[1] In this context, a sulfur-containing motif of sulfides, sulfoxides, and sulfones represents an ideal linker. Consequently, many biologically active compounds and drugs comprise the S-linkers including sulfide (R−S−R′), sulfinyl (R−S(O)−R′), and sulfonyl (R−SO_2−R′) groups (Figure 1).[2−4] In addition, these moieties improve important drug-like parameters: decrease lipophilicity, increase water solubility, and serve as good hydrogen bond acceptors.[4] The S-linkers, however, meet all the criteria except for 3 because suitable synthetic routes to sized libraries of these compounds have remained undiscovered. Considering the above fact, our Parallel Synthesis Department was interested to develop a parallel synthesis approach to alkyl sulfides, sulfoxides, and sulfones, among others:[5−8] having homologues compounds in a library would allow one to compare their activity with geometry and H-bond acceptor features of the S-linkers. The choice of the alkyl derivatives was because of growing interest in compounds with a saturated skeleton:[9−12] sp^3-hybridized carbon atoms next to sulfur atom might increase flexibility of a R−$C_{sp}{}^3$−S−$C_{sp}{}^3$−R′ fragment thus providing a better fitness to a three-dimensional binding pocket of a target protein.

The method under development has to satisfy the following conditions of parallel synthesis: (a) to use stable, inexpensive, nontoxic, and compatible reagents and solvents, (b) to allow for easy preparation of a highly diverse library, and (c) to have straightforward procedure and workup. We initially focused on finding an optimal approach to sulfides, the starting materials in the synthesis of sulfoxides and sulfones.[13] Sulfides are typically synthesized by alkylation of thiols. The latter compounds, however, are foul-smelling and unstable toward oxidation under ambient conditions; their lower homologues are highly volatile and toxic. Alternatively, thiols can be cleanly prepared in situ by reacting thiourea with an appropriate alkylating reagent followed by a hydroxide-mediated decomposition of the intermediary thiuronium salt resulting in a thiolate.[14−17] Subsequent interaction of the thiolate with the second alkylating reagent affords the sulfide. This three-step procedure meets the above conditions: it requires inexpensive reagents: thiourea and alkyl chlorides; provides diverse sets of sulfides by varying the alkylating agents; and allows a one-pot procedure

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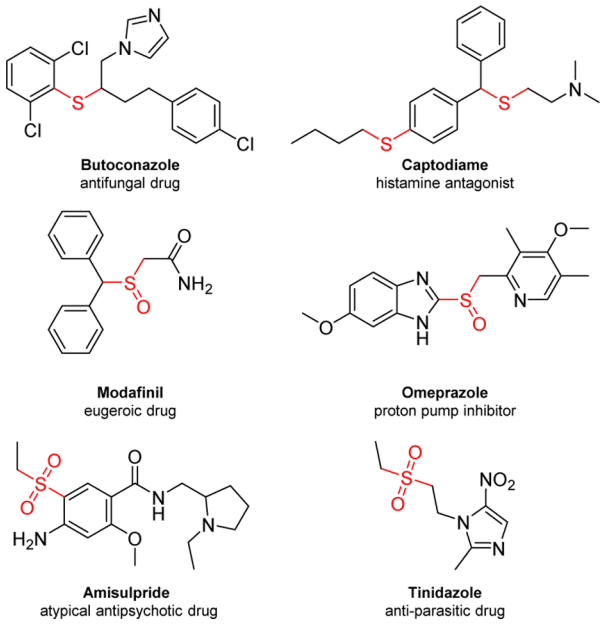


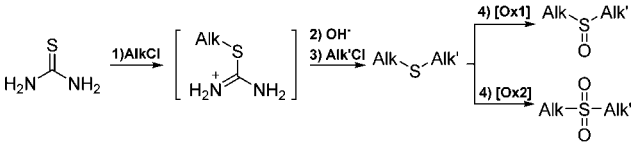
Figure 1. Drugs bearing the S-linkers.[3]

with products of high purity. The method, therefore, has been selected for the parallel synthesis.

Sulfoxides and sulfones are prepared by mono or full oxidation of sulfides. Chemoselectivity of the oxidation depends on the reaction conditions including duration, temperature of the reaction mixture, amount of an oxidizing agent, typically hydrogen peroxide, and the use of a promoter, for example, triflic anhydride, molybdenum(VI) oxide, or 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride.[18−25] Trying to minimize number of reactants, we performed initial oxidation experiments with H_2O_2 varying the oxidant/sulfide ratio. The experiments were successful for the mono oxidation but failed for the full oxidation yielding a complex mixture of sulfide, sulfoxide, and sulfone. Addition of an inexpensive promoter, ammonium molybdate, increased chemoselecivity of the reaction resulting in sulfones as main product.

Combination of the above alkylation and oxidation procedures with further optimization for parallel synthesis allowed us to develop a one-pot approach to alkyl sulfides, sulfoxides, and sulfones starting from thiourea (Scheme 1). Herein, we report the successful employment of this method to the synthesis of an 81 member library of the S-linker bearing compounds.

Scheme 1. One-Pot Approach to Sulfoxides and Sulfones

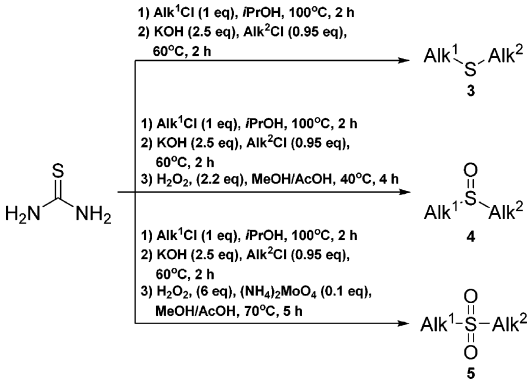


RESULTS AND DISCUSSION

The proposed method utilized a thiourea to sulfide and a sulfide to sulfoxide or sulfide to sulfone transformations. The first transformation included (1) an alkylation of thiourea, (2) a base-catalyzed decomposition of a thiouronium salt, and (3) an alkylation of a thiolate. The second transformation was a mono or full oxidation of the sulfide. The optimization of the procedure was focused on a simple set up, applicability to a wide range of substrates, and provision of high yield and purity of intermediate products at each step. We avoided heterogeneous mixtures under parallel synthesis conditions because presence of insoluble material could affect reaction efficiency and complicate work up.

In the first step, equimolar amounts of thiourea and alkyl chloride **1** reacted at 100 °C for 2 h (Scheme 2). Alkyl

Scheme 2. One-Pot Synthesis of Sulfides (Chemset 3), Sulfoxides (Chemset 4), and Sulfones (Chemset 5) from Thiourea



chlorides were preferred reagents because the halide anions formed upon alkylation of thiourea with alkyl bromides or iodates might halogenate active sites of the products under the reaction conditions. We selected 2-propanol as a solvent for the alkylation: it was compatible with the oxidation step and dissolved the reagents increasing effectiveness of the alkylation. Heating of the reaction mixtures was achieved by placing a rack with the vials in an oven (Figure S2 in the Supporting Information).

We combined the formation and the alkylation of thiolate in one step: to the reaction mixture was added an excess of a base, 4 M KOH solution in methanol, followed by alkyl chloride **2**. KOH was selected on the basis of its solubility in alcohols and efficiency to form thiolates. We found that heating the reaction mixture at 60 °C for 2 h in an ultrasonic bath ensured high conversion to sulfides **3** (Figure S3 in the Supporting Information). By generating an excess of the thiolate (typically 5 mol %) compared to the amount of **2**, we avoided traces of unreacted alkylating reagents, highly undesirable impurities. The unreacted hydrophilic thiolate could be easily washed out with a 2-propanol-water solution after the alkylation step or with water as sulfonate after the oxidation step. If the sulfide was the final product, we quenched the reaction mixture with water upon which the product was typically precipitated out. Otherwise, we diluted the reaction mixture with methanol and added acetic acid followed by an oxidizing agent. The dilution prevented vigorous reaction and spillage of the mixture. The addition of acid was necessary to neutralize the excess base because H_2O_2 decomposes under basic conditions decreasing the efficacy of the oxidation. For the mono oxidation, we utilized an experimentally established amount of H_2O_2 of 2.2 equiv, which was sufficient for the sulfide to sulfoxide transformation resulting in minimal overoxidation. For the full oxidation, higher amounts of H_2O_2 yielded substantial amounts of impurities, primarily unreacted sulfide and sulfoxide

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intermediates. Therefore, we introduced in the synthesis the promoter, $(NH_4)_2MoO_4$, a more soluble and efficient analog of MoO_3. Experimentally established amounts of H_2O_2 of 6 equiv and $(NH_4)_2MoO_4$ of 0.1 equiv allowed us to overcome the issue. The oxidation reactions were conducted in an ultrasonic bath with heating: the mono oxidation at 40 °C for 4 h, the full oxidation at 70 °C for 5 h. Similar to the sulfides, most sulfones precipitated out from the reaction mixtures and were separated by filtration. For sulfoxides and highly soluble sulfones, the work up included solvent evaporation followed by extraction with chloroform.

To validate the method, we selected two sets of alkyl chlorides from our internal database (chemset **1**, Figure 2, and

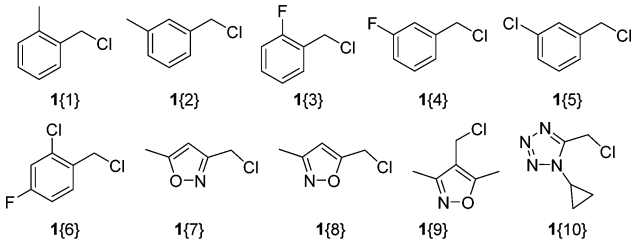

Figure 2. Alkyl chlorides **1**, chemset **1**.

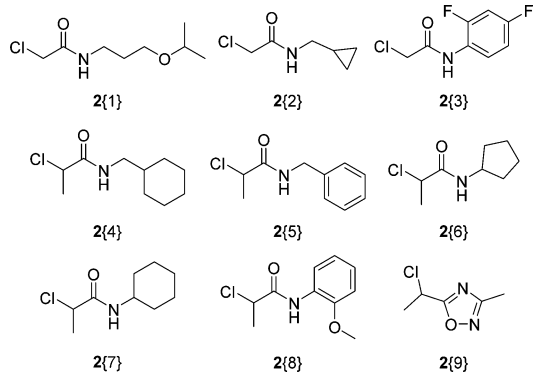

Figure 3. Alkyl chlorides **2**, chemset **2**.

chemset **2**, Figure 3). While selecting the reagents, we omitted alkyl chlorides bearing groups that can be oxidized under the reaction conditions, for example, aryl iodide, derivatives of pyrrole, indole, and furane. Despite the possibility to alter alkyl chlorides **1** and **2** at the devirsity-responsible alkylation step, we assigned amides of chloracetic acid to the chemset **2**. These amides formed unstable thiuronium salts which would decrease purity of the products but smoothly reacted with the preformed thiolates resulting in corresponding sulfides. Then, we performed 81 one-pot parallel reactions, 3 transformations per a pair of the alkyl chlorides: to sulfide, to sulfoxide, and to sulfone (Table 1) [synthesis of a full combinatorial set (270) was beyond the scope of this work]. Since biochemical assays typically require a milligram quantity of a test compound, we carried out the reactions on a millimolar scale in 8 mL sealed vials (Figure S1, in the Supporting Information).

The analysis of crude samples allowed us to assess the efficacy of the experimental procedure (Figures S4−S63, in the Supporting Information): most synthesized compounds were obtained in good to high yield with acceptable purity (more than 90%). Only in 28% of the experiments purification by flash chromatography was required, which negatively influenced the isolated yields. Despite this necessity for some compounds, the obtained quantities of the products exceeded 30 mg which is sufficient for biochemical assays. The identities and purities of all synthesized compounds were confirmed by ^1H and ^{13}C NMR spectroscopy and LC−MS analysis.

We also evaluated our optimized method on a small-scale synthesis of 2-(benzhydrylsulfinyl)acetamide (modafinil) (Figure 1, Scheme 3). The resulting yield of 45% was on par with that reported for modafinil in the previously published procedures.[26−28]

In conclusion, we describe in the current paper a one-pot parallel synthesis approach to the compounds with the S-linkers of different geometry: alkyl sulfides, sulfoxides, and sulfones. The method was based on two transformations: alkylation of thiourea to produce sulfides and mono or full oxidation of sulfides to produce sulfoxides or sulfones. The transformations were optimized to the conditions of parallel synthesis to utilize (1) simple set up and basic labware, an oven and an ultrasonic bath; (2) inexpensive and readily available reagents, thiourea, alkyl chlorides, H_2O_2 and $(NH_4)_2MoO_4$; and (3) straightforward workup, filtration or extraction. The above features allow one to easily generate large libraries of S-linkers. We demonstrated the successful employment of the approach on the 81-member library of alkyl sulfides, sulfoxides, and sulfones and on a small-scale synthesis of 2-(benzhydrylsulfinyl)-acetamide which resulted in the products on a 30−300 mg scale.

Understanding the established impact of sulfides, sulfoxides, and sulfones in drug discovery[3,29] and the recent popularity of saturated compounds,[9] we believe that our method will be useful to scientists dealing with combinatorial synthesis of these molecules and allow to expand their variety.

EXPERIMENTAL PROCEDURES

All chemicals and solvents were obtained from commercially available sources (Enamine, Sigma-Aldrich) and used without further purification. ^1H and ^{13}C NMR spectra were acquired on Bruker Avance DRX 500 spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on PerkinElmer Spectrum BX II. Melting points were determined on a Buchi melting point apparatus and are uncorrected. LC-MS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector, column: Zorbax SB-C18, 4.6 mm × 15 mm. Eluent, A, acetonitrile−water with 0.1% of TFA (95:5); B, water with 0.1% of TFA. The purification of the compounds was performed using a Companion Combi-Flash instrument with UV-detector and a reusable LukNova column [eluent, A, $CHCl_3$; B, $CHCl_3$/methanol (7:3, v:v)].

General Procedure for the Synthesis of Sulfides (3). A mixture of thiourea (1 mmol) and an alkylating agent **1** (1 mmol) in 0.6 mL of 2-propanol was heated for 2 h at 100 °C in an 8 mL sealed vial. After it was cooled to room temperature, KOH (2.5 mmol) as 4 M solution in methanol and an alkylating agent **2** (0.95 mmol) were added sequentially to the reaction vial. The obtained mixture was heated for 2 h at 60 °C in an ultrasonic bath. Sulfides **3** typically precipitated out from the solution upon cooling the reaction mixture to room temperature. The substantial filtration and drying of the precipitate resulted in the product. In other cases, chloroform (3 mL) and water (7 mL) were added and the organic phase was washed with water (7 mL), separated, and evaporated to

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Table 1. Synthesized Library of the S-Linker Compounds

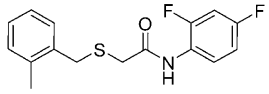
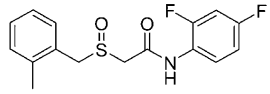
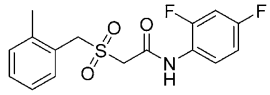
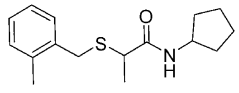
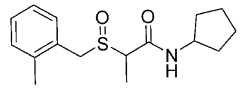
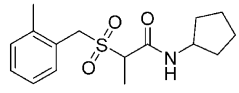
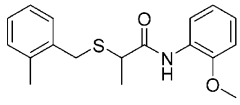
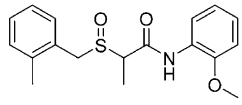
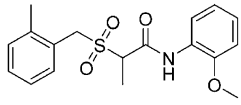
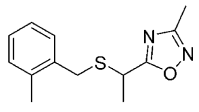
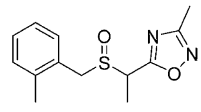
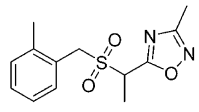
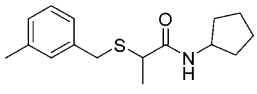
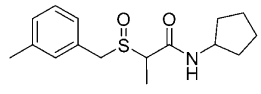
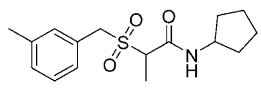
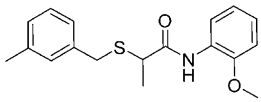
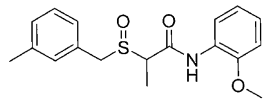
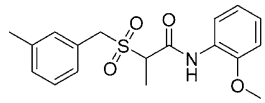
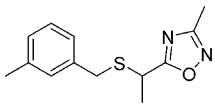
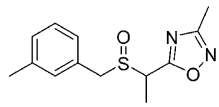
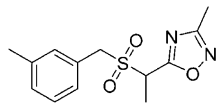
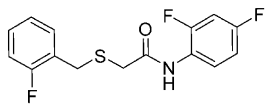
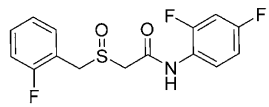
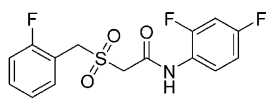
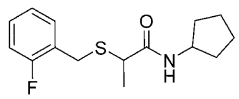
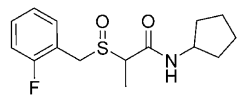
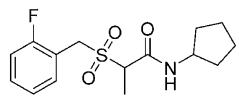
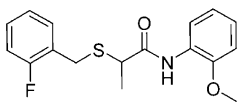
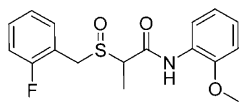
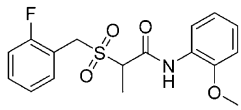
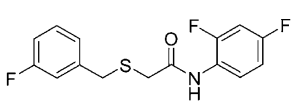
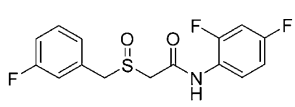
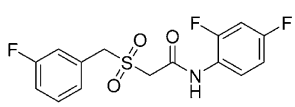
Sulfide **3**	Yield[a] (%)	Sulfoxide **4**	Yield[a] (%)	Sulfone **5**	Yield[a] (%)
 **3**{1,3}	80	 **4**{1,3}	78	 **5**{1,3}	48
 **3**{1,6}	90	 **4**{1,6}	89	 **5**{1,6}	45
 **3**{1,8}	95	 **4**{1,8}	89	 **5**{1,8}	81
 **3**{1,9}	67	 **4**{1,9}	47	 **5**{1,9}	57
 **3**{2,6}	62	 **4**{2,6}	79	 **5**{2,6}	38
 **3**{2,8}	24	 **4**{2,8}	33	 **5**{2,8}	5
 **3**{2,9}	73	 **4**{2,9}	35	 **5**{2,9}	90
 **3**{3,3}	89	 **4**{3,3}	74	 **5**{3,3}	77
 **3**{3,6}	84	 **4**{3,6}	85	 **5**{3,6}	63
 **3**{3,8}	89	 **4**{3,8}	94	 **5**{3,8}	66
 **3**{4,3}	30	 **4**{4,3}	64	 **5**{4,3}	44

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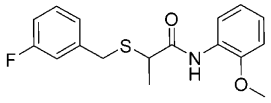
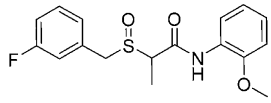
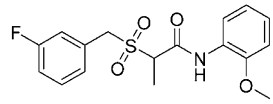
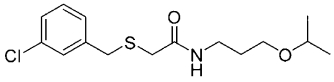
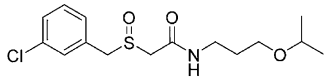
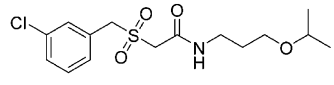
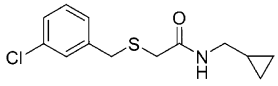
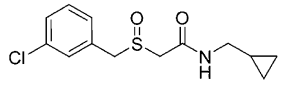
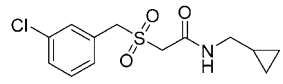
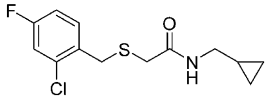
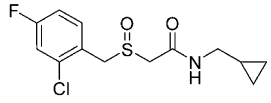
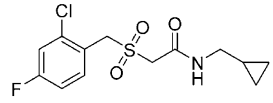
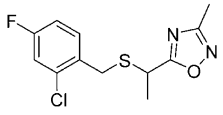
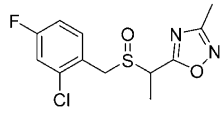
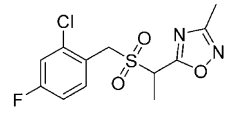
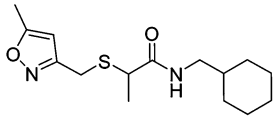
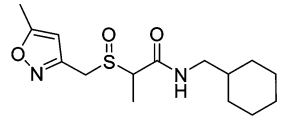
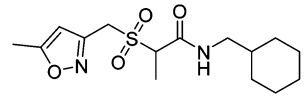
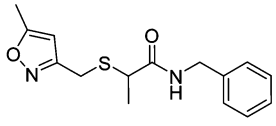
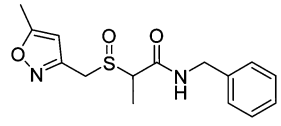
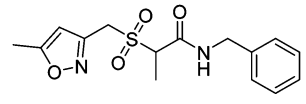
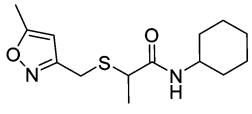
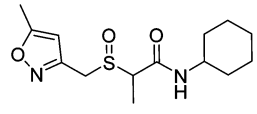
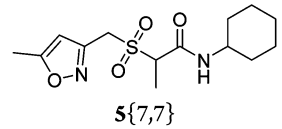
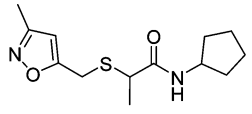
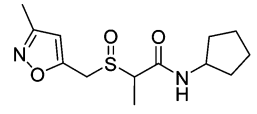
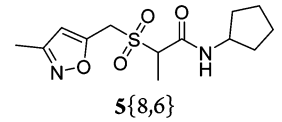
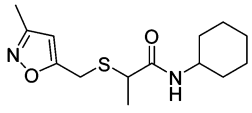
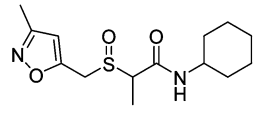
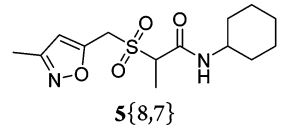
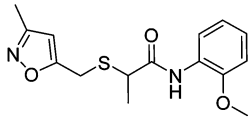
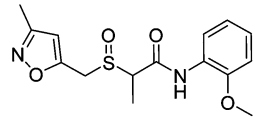
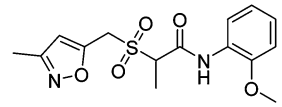
Table 1. continued

Sulfide **3**	Yield[a] (%)	Sulfoxide **4**	Yield[a] (%)	Sulfone **5**	Yield[a] (%)
 **3**{4,8}	55	 **4**{4,8}	38	 **5**{4,8}	42
 **3**{5,1}	92	 **4**{5,1}	82	 **5**{5,1}	27
 **3**{5,2}	35	 **4**{5,2}	80	 **5**{5,2}	59
 **3**{6,2}	30	 **4**{6,2}	64	 **5**{6,2}	44
 **3**{6,9}	87	 **4**{6,9}	38	 **5**{6,9}	42
 **3**{7,4}	64	 **4**{7,4}	49	 **5**{7,4}	68
 **3**{7,5}	82	 **4**{7,5}	42	 **5**{7,5}	59
 **3**{7,7}	38	 **4**{7,7}	19	 **5**{7,7}	43
 **3**{8,6}	77	 **4**{8,6}	53	 **5**{8,6}	40
 **3**{8,7}	27	 **4**{8,7}	10	 **5**{8,7}	33
 **3**{8,8}	75	 **4**{8,8}	90	 **5**{8,8}	36

[a]Isolated yield.

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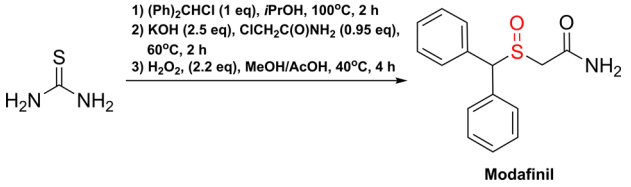
Scheme 3. One-Pot Synthesis of 2-(Benzhydrylsulfinyl)acetamide



yield a crude **3**. If the product had purity below 90%, it was purified using flash chromatography.

General Procedure for the Synthesis of Sulfoxides (4) and Sulfones (5). A mixture of thiourea (1 mmol) and an alkylating agent **1** (1 mmol) in 0.6 mL of 2-propanol was heated for 2 h at 100 °C in an 8 mL sealed vial. After it was cooled to room temperature, KOH (2.5 mmol) as 4 M solution in methanol and an alkylating agent **2** (0.95 mmol) were added sequentially to the reaction vial. The obtained mixture was heated for 2 h at 60 °C in an ultrasonic bath. After it was cooled to room temperature, the mixture was diluted with methanol (3 mL) and acidified with acetic acid (0.175 mL). Then, an oxidant was added: H_2O_2 (2.2 mmol, 0.175 mL of 50% solution in H_2O) for the mono oxidation or H_2O_2 (6 mmol, 0.45 mL of 50% solution in H_2O) and $(NH_4)_2MoO_4$ (0.1 mmol, 0.175 mL, 10% solution in H_2O) for the full oxidation. The mixture was heated for 4 h at 40 °C (the mono oxidation) or for 5 h at 70 °C (the full oxidation) in the ultrasonic bath. Crude sulfoxide **4** and highly soluble sulfones **5** were obtained after treating the reaction mixture with chloroform (3 mL) and water (7 mL) and substantial separation and evaporation of organic phase. Sulfones **5** typically precipitated out from the solution upon cooling the reaction mixture to room temperature. The filtration and drying of the precipitate resulted in the product. If the product had purity below 90%, purification was performed using flash chromatography.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental set up, LC-MS data, ^1H and ^{13}C NMR spectra, and spectral data for the selected synthesized compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00024.

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Notes

The authors declare no competing financial interest.

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