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Letter

Chemoselective α-Sulfidation of Amides Using Sulfoxide Reagents

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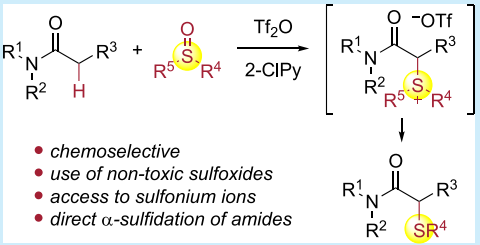
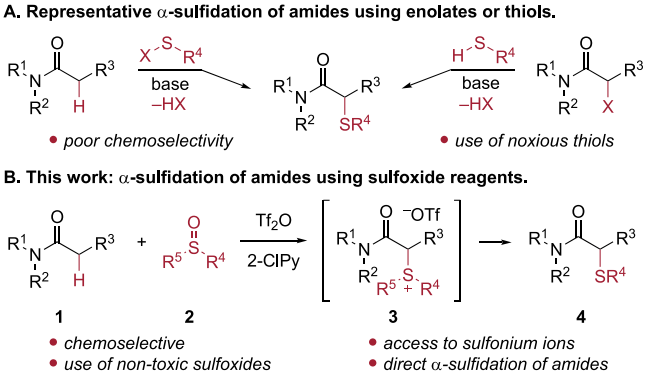
ABSTRACT: The direct α-sulfidation of tertiary amides using sulfoxide reagents under electrophilic amide activation conditions is described. Employing convenient and readily available reagents, selective functionalization takes place to generate isolable sulfonium ions en route to α-sulfide amides. Mechanistic studies identified activated sulfoxides as promoters of the desired transformation and enabled the extension of the methodology from benzylic to aliphatic amide substrates.



New methods for the introduction of carbon–sulfur bonds are of interest in the synthesis and diversification of bioactive compounds given the existence of hundreds of sulfur-containing structures approved by the U.S. Food and Drug Administration for the treatment of human ailments.[1−3] Existing methods for the α-sulfidation of amides rely on nucleophilic displacement, either through the use of basic conditions to activate the amide for nucleophilic attack or α-electrophiles in combination with nucleophilic thiols (Scheme 1A).[4] As an outgrowth of our studies concerning electrophilic amide activation for practical carbon–carbon and carbon–nitrogen bond-forming reactions,[5,6] we recognized an opportunity to develop an orthogonal approach compared with contemporary methods for the introduction of carbon–sulfur bonds. Herein we describe the direct, chemoselective α-sulfidation of amides using sulfoxide reagents (Scheme 1B).

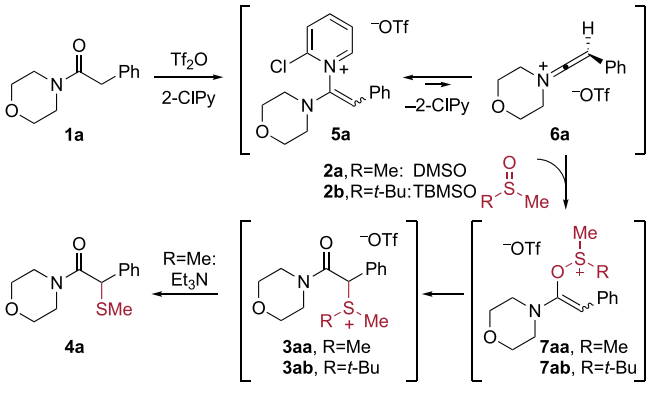
Scheme 1. Methods for the α-Sulfidation of Amides



We have previously demonstrated[5,6] that the reagent combination of trifluoromethanesulfonic anhydride (Tf_2O) and a substituted pyridine such as 2-chloropyridine (2-ClPy)[7] is effective for electrophilic amide activation[8] to enable the addition of various nucleophiles. Innovative reports continue to demonstrate the practical nature of this approach to amide derivatization.[9,10] Inspired by observations on the addition of pyridine *N*-oxides to activated amides,[11] as in our modified Abramovitch reaction that leads to carbon–nitrogen bond formation,[5e] and the use of sulfoxides in carbon–carbon bond formation,[9j] we envisioned the use of sulfoxide reagents for carbon–sulfur bond formation. Sulfoxides are readily available, easily derivatized, and bench stable in comparison with noxious thiols and can serve as both an oxidant and a sulfur source.[12,13]

We anticipated that the addition of dimethyl sulfoxide (DMSO, **2a**) upon the electrophilic activation of amide **1a** would lead to oxysulfonium ion **7aa** en route to α-sulfonium amide **3aa**, which could afford α-sulfide amide **4a** after demethylation (Scheme 2). Under optimal conditions,[14] the

Scheme 2. α-Sulfidation of Benzylic Amide 1a



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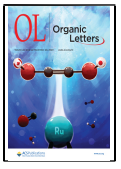

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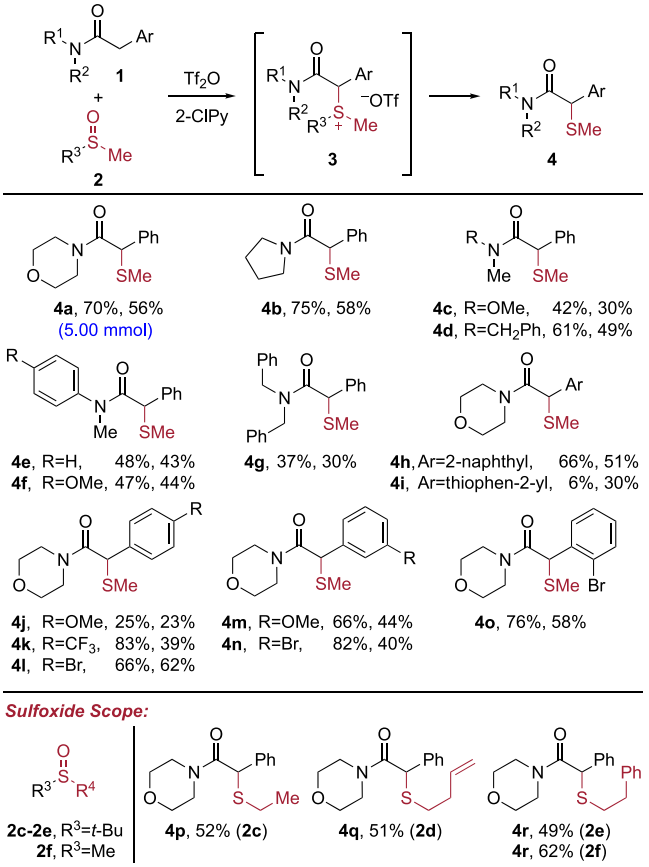
activation of amide **1a** with Tf_2O (1.05 equiv) and 2-ClPy (3.00 equiv) followed by the addition of DMSO (1.20 equiv) gave complete sulfoxide addition and conversion to α-sulfonium amide **3aa** at −30 °C without the observation of any persistent intermediates by *in situ* IR.[15] The exposure of sulfonium ion **3aa** to excess triethylamine in acetonitrile at 60 °C subsequently led to quantitative demethylation[16] and afforded α-sulfide amide **4a** (67% yield, two steps). Furthermore, a single-step procedure was also developed wherein the use of *tert*-butyl methyl sulfoxide (TBMSO, **2b**) as the sulfidation reagent enabled direct access to sulfide **4a** in 54% yield via the spontaneous dealkylation of α-sulfonium amide **3ab**.

The application of this chemistry to the α-sulfidation of α-aryl acetamides is illustrated in Scheme 3. Sulfide **4a** could be prepared on a 5.00 mmol scale without compromising the reaction efficiency via either the two-step procedure (Method A: 70% yield) or the single-step procedure (Method B: 56% yield). A variety of α-aryl acetamides including versatile morpholine-derived amides (**4a** and **4h**−**4o**),[17] in addition to *N*-methoxy- (**4c**),[18] *N*-phenyl- (**4e** and **4f**), and *N*-benzyl-substituted (**4d** and **4g**) amides, served as substrates for this transformation.[19,20] Substituents that may compromise the stability of the α-sulfonium ion intermediate **3** led to low isolated yields of the desired product (**4i** and **4j**). When demethylation was omitted, dimethylsulfonium trifluoromethanesulfonates **3aa** and **3ba** derived from morpholine and pyrrolidine amides **1a** and **1b** could be isolated in 61 and 68% yield, respectively.[14]

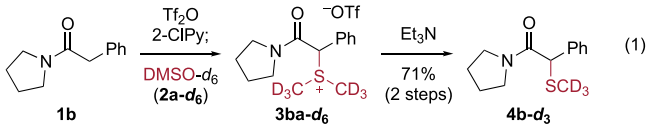
Scheme 3. α-Sulfidation of Benzylic Amides[a]

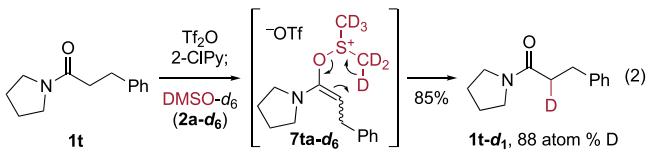


[a]Reagents and conditions: Method A (methyl sulfoxides): Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, −78 → 0 °C, 15 min; methyl sulfoxide (**2a**, **2f**, 1.20 equiv), CH_2Cl_2, −78 → 22 °C, 45 min; Et_3N (10 equiv), MeCN, 60 °C, 15 h. Method B (*tert*-butyl sulfoxides): Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, −78 → 0 °C, 15 min; *tert*-butyl sulfoxide (**2b**−**2e**, 1.20 equiv), CH_2Cl_2, −78 → 22 °C, 45 min. Yields are reported: Method A, Method B.

Employing our single-step sulfidation procedure, we also examined the use of other *tert*-butyl sulfoxides **2c**−**2e** with amide **1a** to give the corresponding α-sulfide amides **4p**−**4r**.[14] In each case, the primary alkyl substituent of the *tert*-butyl sulfoxide was preserved, owing to the relative stability of the cation derived from the *tert*-butyl substituent in the spontaneous dealkylation. Complimentarily, α-sulfide amide **4r** was also obtained in 62% yield with methyl sulfoxide **2f** after regioselective dealkylation, leaving the homobenzylic substituent intact. Whereas the two-step procedure generally affords higher yields, *tert*-butyl sulfoxides directly form the α-sulfide amides. Additionally, the use of *tert*-butyl sulfoxides enables the sulfidation of substrates where the α-sulfonium ion intermediate is subject to hydrolysis (e.g., sulfidation of α,α-diphenyl acetamide **S1** to α-thiomethyl amide **S4**).[14]

In evaluating the scope of the transformation, we found that the conditions described in Scheme 3 were not compatible with amides other than α-aryl acetamides. We therefore pursued a series of mechanistic experiments to guide our efforts to expand the substrate scope of our amide sulfidation methodology. Whereas the use of DMSO-d_6 (**2a**-d_6) for the α-sulfidation of benzylic amide **1b** led to α-sulfide amide **4b**-d_3 in 71% yield (eq 1), when DMSO-d_6 (**2a**-d_6) was used with aliphatic amide **1t**, we only observed the recovery of tertiary amide **1t**-d_1 (85% yield) with 88 atom % D incorporation at the α-position (eq 2).[14] We attributed these observations to a retro-ene reaction from intermediate **7ta**-d_6 that is preferred for aliphatic substrates.[21,22]





Toward our goal of the mechanism-guided expansion of the scope of our α-sulfidation chemistry, it was necessary to develop a detailed understanding of the underlying sulfidation pathway. We envisioned that oxysulfonium ion intermediate **7**, derived from the addition of sulfoxide to keteniminium **6**, undergoes rearrangement to give the α-sulfonium amide **3**. Both intra- and intermolecular pathways for 1,3-sulfur shifts were identified by Kwart for neutral sulfides,[23] and we have previously described an intramolecular pathway in our modified Abramovitch reaction.[5e] In contrast with these existing proposals, we identified a distinct intermolecular sulfidation pathway supported by density functional theory (DFT) calculations, wherein an electrophilically activated sulfoxide **8**[24] transfers the sulfonium moiety via a cyclic transition state (Scheme 4).

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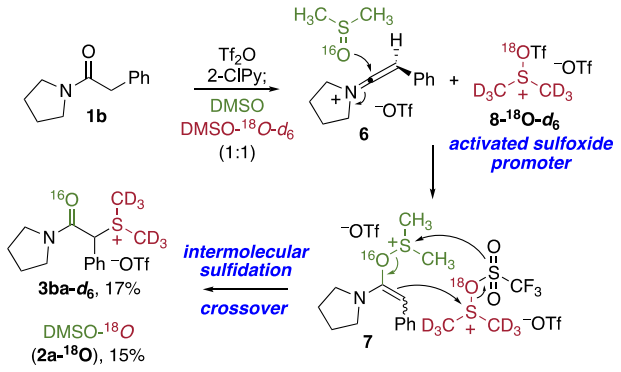
Scheme 4. Proposed Intermolecular Sulfidation Pathway



- *all possible crossover and non-crossover products observed*
- *activated sulfoxide* **8** *promotes desired sulfidation over retro-ene pathway*
- *supported by DFT calculations*

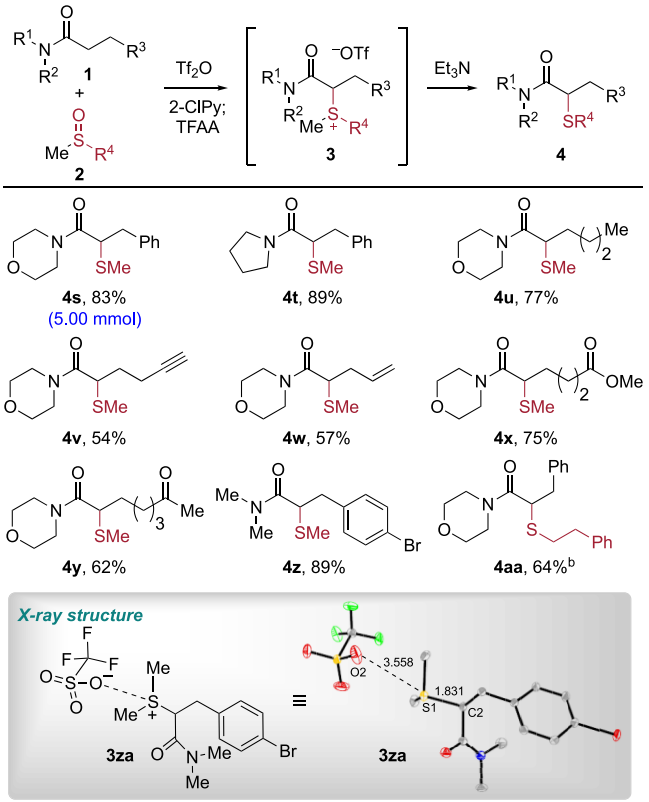
Distinguishing intra- and intermolecular sulfidation pathways was accomplished by means of a crossover experiment employing an equal mixture of DMSO (**2a**) and doubly labeled DMSO-^{18}O-d_6 (**2a**-^{18}**O**-d_6). When amide **1b** was subjected to the standard reaction conditions using this sulfoxide mixture, we observed the substantial formation of crossover sulfonium ion products **3ba**-^{18}**O**/**3ba**-d_6 and DMSO (**2a**-^{18}**O**/**2a**-d_6) by quadrupole time-of-flight (Q-TOF) mass spectrometry,[14] consistent with our proposed intermolecular pathway.[25,26] Notably, crossover in the recovered sulfoxide is inconsistent with a separate intermolecular pathway akin to Kwart's,[23] involving the combination of two oxysulfonium ions **7**.[27]

In considering other intermolecular pathways, we sought to distinguish our mechanistic proposal from existing α-sulfidation methods that rely on nucleophilic displacement (Scheme 1A).[4] Accordingly, when nucleophilic dimethyl sulfide-d_6 (1.00 equiv) was added to the reaction mixture at −78 °C, we observed unsubstantial deuterium incorporation into sulfonium product **3aa**.[28] Furthermore, DFT calculations identified a relatively high barrier for sulfur−oxygen cleavage from oxysulfonium ion **7** to form the requisite nucleophile−electrophile pair.[14]

Our mechanistic insights suggested that the unproductive retro-ene pathway that initially precluded the α-sulfidation of aliphatic amide **1t** may be outcompeted by increasing the concentration of electrophilically activated sulfoxide **8**. Indeed, the α-sulfidation of amide **1t** with DMSO proceeded in 79% yield by increasing the amount of sulfoxide used and adding supplemental Tf_2O after amide activation, consistent with our mechanism-based hypothesis. Compared with other oxidants employed in amide activation protocols,[4g] our results collectively establish that sulfoxides serve additional roles as sulfur sources *and* promoters in this unique transformation.

The further evaluation of sulfoxide activators revealed that trifluoroacetic anhydride (TFAA) offered the sulfidated aliphatic amides in higher yield compared with Tf_2O.[14,29] This rationally modified protocol provided access to a variety of α-sulfidated aliphatic amides (Scheme 5, Method C).[30,31] The α-sulfidated morpholine amide **4s** could be prepared on a 5.00 mmol scale with similar reaction efficiency to saturated α-sulfide amides **4t** and **4u**. Terminal alkyne **1v**, alkene **1w**, and ester- and ketone-containing substrates **1x** and **1y** could be chemoselectively sulfidated adjacent to the amide group, even in the presence of other unprotected carbonyl groups. Aliphatic amide **1aa** was sulfidated using methyl sulfoxide

Scheme 5. α-Sulfidation of Aliphatic Amides[a]



[a]Reagents and conditions, Method C: Tf_2O (1.10 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, −78 → 0 °C, 15 min; DMSO (**2a**, 2.50 equiv), TFAA (1.00 equiv), CH_2Cl_2, −78 → 22 °C, 45 min; Et_3N (10 equiv), MeCN, 60 °C, 15 h. [b]Sulfoxide **2f** (2.50 equiv).

derivative **2f** after regioselective dealkylation. For amide **1z**, single crystals suitable for X-ray diffraction were obtained of intermediate **3za**[32] en route to α-sulfide product **4z**, revealing a noncovalent interaction[33] between the sulfonium cation and the trifluoromethanesulfonate anion that underlies its high solubility in organic solvents and resistance toward elimination and hydrolysis.[34]

In conclusion, we have identified a direct procedure for the chemoselective α-sulfidation of amides. This transformation is applicable to a wide range of tertiary amides with high functional group tolerance. The use of convenient and easily accessible sulfoxides enhances the practicality of this strategy and enables the single-step functionalization of benzylic amides via spontaneous dealkylation. Our ability to sulfidate α-aryl acetamides and introduce small thioalkyl groups, otherwise derived from exceptionally noxious thiols, is unparalleled in comparison to existing amide activation protocols.[4g] Mechanistic studies supported the role of electrophilically activated sulfoxides as promoters for the sulfidation and enabled the extension of the methodology to aliphatic tertiary amide substrates. Overall, this approach offers a valuable alternative to existing solutions for the α-sulfidation of amides by introducing an orthogonal strategy under mild conditions and provides direct access to functionalized amides for fine chemical synthesis.[1−3]

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03160.

Experimental procedures, spectroscopic data, computed free energy profiles, Cartesian coordinates, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 1916405 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

†M.L. and K.A.D. contributed equally.

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Notes

The authors declare no competing financial interest.

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(25) When a substoichiometric quantity of Tf_2O was used in the crossover experiment (0.50 equiv), the proportion of crossover products **3ba**-^{18}**O**/**3ba**-d_6 observed was diminished. This is consistent with the predominance of an intramolecular pathway in the absence of activated sulfoxide promoter **8** rather than an intermolecular pathway.

(26) The use of enantiomerically enriched sulfoxide (−)-**2b** in the sulfidation of amide **1a** gave racemic product **4a**.

(27) The complete transfer of the oxygen from the sulfoxide to the sulfidated product was verified by the reaction of amide **1b** with DMSO-^{18}O-d_6 (**2a**-^{18}**O**-d_6). Thus the *in situ* formation of crossover DMSO (**2a**-^{18}***O***/**2a**-d_6) via the ^{16}O/^{18}O exchange of the sulfoxide with unlabeled Tf_2O/TfO^- does not occur prior to sulfidation.

(28) The distribution of sulfonium products **3ba** and **3ba**-d_6 was 76 and 24%, respectively. The observation of the partial formation of **3ba**-d_6 is consistent with competitive reversible oxygen transfer from electrophilically activated sulfoxides to sulfides; see: Tanikaga, R.; Nakayama, K.; Tanaka, K.; Kaji, A. Reversible Oxygen Transfer Reactions between Sulfoxides and Sulfides. Relative Stabilities of Acyloxysulfonium Ions. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3089−3090.

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(30) Replacing DMSO (**2a**) with TBMSO (**2b**) in Method C resulted in decreased yields of α-sulfidated amides. We hypothesize that TBMSO, upon electrophilic activation, is subject to spontaneous dealkylation of the *tert*-butyl group to give a sulfenate; see: (a) Yoshimura, T.; Tsukurimichi, E.; Yamazaki, S.; Soga, S.; Shimasaki, C.; Hasegawa, K. Synthesis of a stable sulfenic acid, *trans*-decalin-9-sulfenic acid. *J. Chem. Soc., Chem. Commun.* **1992**, 1337−1338. (b) Okuyama, T.; Fueno, T. Acid-Catalyzed Cleavage of Methoxymethyl Phenyl Sulfoxide. Solvent Effects and Mode of Bond Cleavage. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3111−3116.

(31) The starting aliphatic amides, derived from the competing retro-ene pathway, were recovered (∼15%) in most cases.

(32) Sulfonium trifluoromethanesulfonate **3za** can be stored at 22 °C for weeks. It can be demethylated by treatment with triethylamine according to our standard conditions to give sulfide **4z** in 92% yield.

(33) The noncovalent interaction is evidenced by the considerable elongation of the Me_2S^+−C bond: 1.831 Å. Additionally, the oxygen atom of the longest S−O bond in the trifluoromethanesulfonate anion is engaged in this interaction (1.444 Å vs 1.428, 1.425 Å). For a similar discussion, see: Lodochnikova, O. A.; Litvinov, I. A.; Palei, R. V.; Plemenkov, V. V. Crystal structure of the sulfonium salts of natural azulenes. *J. Struct. Chem.* **2008**, *49*, 322−326.

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