Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Palladium-Catalyzed Thiomethylation via a Three-Component Cross-Coupling Strategy

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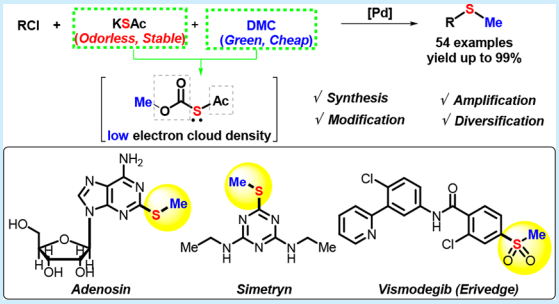
Supporting Information

ABSTRACT: In this report, the combination of masked inorganic sulfur and dimethyl carbonate was designed to achieve thiomethylated cross coupling of aryl chlorides. Remarkably, this powerful strategy realized thiomethylation of nucleosides bearing unprotected ribose, chloride-containing pharmaceuticals with late-stage coupling, and herbicides possessing multiple heteroatoms and steric hindrance. Moreover, this protocol is practically amenable to multigram-scale synthesis with a lower catalysis loading and a higher yield.



Organosulfur chemistry is gaining more and more significance since carbon−sulfur bonds are continuously ubiquitous in biological molecules,[1] pharmaceuticals,[2] and agrochemicals.[3] Sulfur-containing molecules have been commonly and widely applied in antibacterials, antiviral, and anticancer since the establishment of the U.S. Food and Drug Administration (FDA) in the early 20th century.[4] Aryl methyl sulfide, sulfoxide, and sulfone motifs are of great significance in modern pharmaceutical science; these are used in compounds such as the antipsychotic drug Thioridazine[5] (Novartis), the cardiovascular drug Sulmazole[6] (Roche), the basal-cell carcinoma drug Vismodegib[7] (Roche), the proliferative diseases drug Thiocolchicine,[8] the nonsteroidal anti-inflammatory drug Sulindac[9] (Merck), and the nonsteroidal anti-inflammatory drug Firocoxib[10] (as illustrated in Figure 1A). Conventionally, the application of methylthiol is the most common pathway for the "MeS" functional group,[11] which is introduced through nucleophilic substitution with only electron-deficient substrates or the methylation of thiols.[12] However, intractable problems[13] associated with catalysts poisoning, oxidation compatibility, and environmental pollution were found from thiols adoption (Figure 1B). Methanethiol, which is a hazardous and fetid gas, possessing low coupling reactivity with aryl halide, because of strong coordination to the transition-metal catalysts, causes terrible risks during the manufacturing process. Alternative sodium methyl mercaptide is formed during coupling in aqueous solution at a maximum concentration of 20%, which impedes the application of association with water compatibility.[14] In the catalytical cycle of the coupling with aryl halide, the bond energy of Pd−SMe (bond dissociation energy (BDE) of 92−99 kcal mol^{-1}) is higher than C_{Ar}−SMe bond cleavage (BDE = 82−85 kcal mol^{-1}),[15] which challenges the reductive elimination process. With the concept of masked sulfurating strategies in our group,[16] we envision that a masked group on inorganic sulfur will drastically decrease the BDE of Pd−S, which realize the C_{Ar}−S bond formation in the cross coupling. Meanwhile, dimethyl carbonate (DMC)[17] decreases the electron cloud density of sulfur with carbonic ester, which will be an ideal methylating agent with depressed catalysis poison. Herein, we report an efficient thiomethylation strategy for the construction of diverse functionalized aryl methyl sulfides via a palladium-catalyzed three-component cross coupling (Figure 1C).

Modern drug discovery relies on the rapid late-stage modification approach and preparation of a panel of structurally related derivatives.[18] Therefore, our initial study focused on the thiomethylation of chlorine-containing pharmaceuticals with miscellaneous sensitive functional groups. We commenced our study with Fenofibrate[19] **1a**, potassium thioacetate,[20] and DMC, under the assistance of palladium catalyst and potassium *tert*-butyloxide, affording an 84% yield of methylthioarene **2a**. Deutero-dimethyl carbonate was explored, affording deuterium product **2a′** in a yield of 77%, which undoubtly demonstrated that DMC served as a green methyl source (see the Supporting Information (SI)).

Under the optimized conditions, different types of aryl halides were comprehensively investigated (see Scheme 1). Substrates bearing Csp^2−I, Csp^2−Br, and even Csp^2−Cl on the phenyl ring could afford desired product with excellent yields. The method is compatible with both single-substituted aryl molecules (**2b**−**2g**) and multiple functional group substituted (**2h**−**2k**). Electron-donating substituents were proven to be entirely compatible in various positions when sodium thiosulfate is employed as the sulfur source, instead of potassium thioacetate

Received: August 21, 2018

DOI: 10.1021/acs.orglett.8b02677
Org. Lett. XXXX, XXX, XXX−XXX

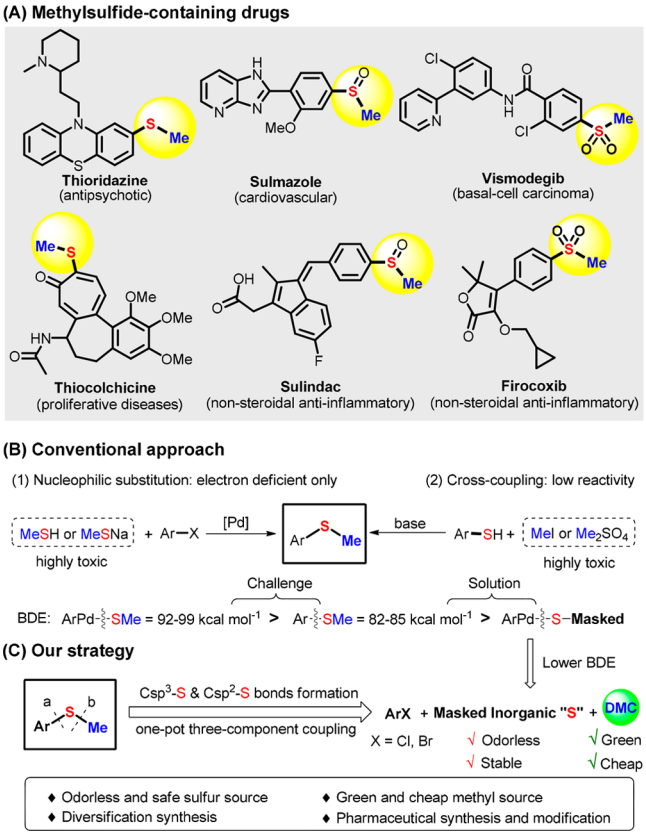
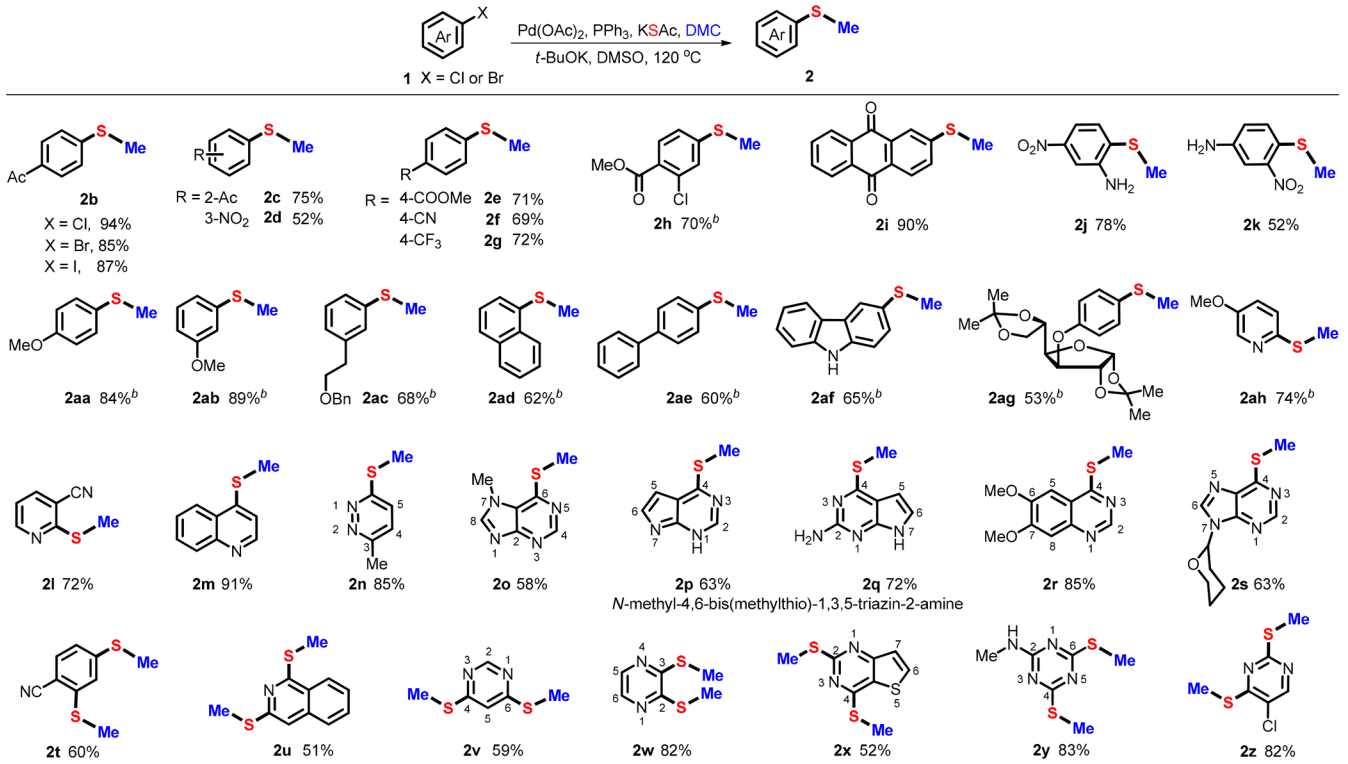


Figure 1. Siginificant methylsulfides.

(**2aa**−**2ah**). Note that a sugar-containing structure was perfectly tolerated, affording the desired thiomethylation product **2ag**. Notably, thiomethylation of heteroaromatics led to the formation of desired products in good to excellent yields under the standard conditions. A variety of heteroaromatic chlorides, such as pyridine **2l**, quinoline **2m**, pyridazine **2n**, purine **2o**, and 1*H*-pyrrolo[2,3-*d*]pyrimidine **2p** were competent coupling partners. 7*H*-pyrrolo[2,3-*d*]pyrimidine with free amino group **2q** was well-tolerated in this transformation. Methoxyl groups at the 6-position and 7-position on quinazoline were tolerated and afforded **2r** in an 85% yield. In particular, 6-chloropurine substituted by pyran on *N*1 position, afforded desired product **2s** successfully. Dihalides with two active reaction sites are also excellent candidates, both aromatic product (**2t**) and aromatic heterocyclic products (isoquinoline **2u**, pyrimidine **2v**, pyrazine **2w**, thieno[3,2-*d*]pyrimidine **2x**, and 1,3,5-triazine **2y**) were generated via dithiomethylation reactions.

The application on 1,3,5-triazine demonstrates the potential utility of this methodology for the synthesis of pesticide scaffolds. A nucleoside,[21] consisting of a nucleobase and a five-carbon sugar, is a significant building block for DNA and RNA, which crucially expresses genetic information.[22] Because of the great compatibility and applicability, we commenced our thiomethylation with the unprotected nucleoside (see Scheme 2). When 2-chloro-adenosin without any protection on ribose and amino group was subjected to the standard conditions, thiomethylation product **3a** could be successfully afforded in a 77% yield, which was further confirmed via single-crystal study (see the SI). Thus, it is possible that the thiomethylated method

Scheme 1. Thiomethylation of Various Aryl Halides[a]



[a]Condition A: X = Cl, **1** (0.2 mmol), KSAc (0.6 mmol), DMC (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), *t*-BuOK (0.6 mmol), and DMSO (2.0 mL) at 120 °C. [b]Condition B: X = Br, **1** (0.1 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (0.2 mmol), DMC (0.5 mmol), $Pd(acac)_2$ (10 mol %), $P^tBu_3{\cdot}HBF_4$ (20 mol %), *t*-BuOK (0.2 mmol), TBAB (0.3 mmol), and DMSO (1.0 mL) at 120 °C.

DOI: 10.1021/acs.orglett.8b02677
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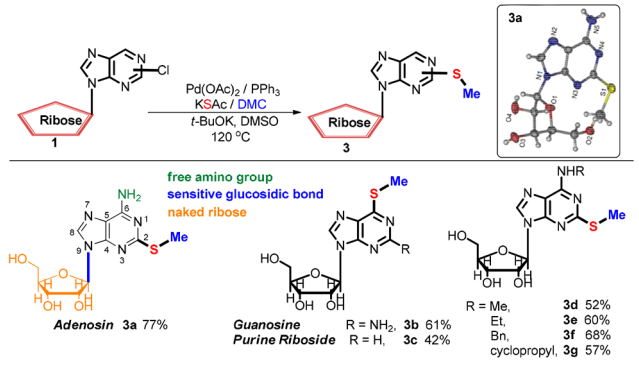
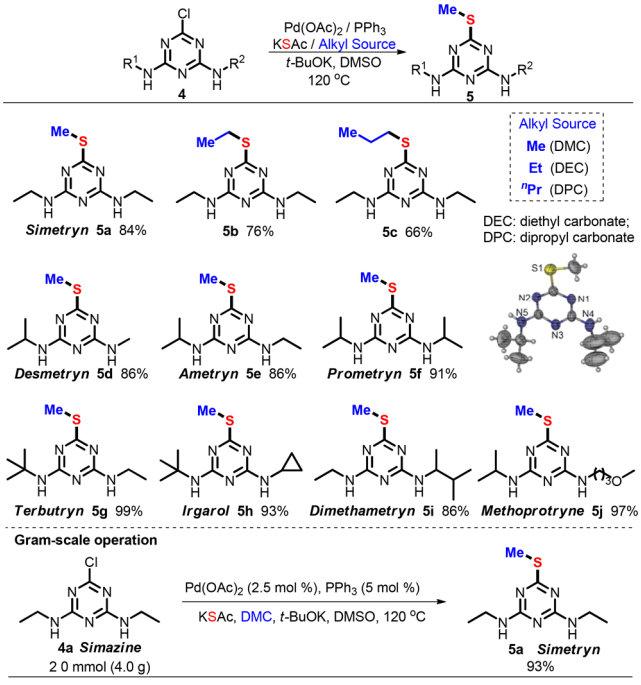
Scheme 2. Thiomethylation on Nucleosides



will provide a straightforward approach to modify DNA and RNA with sulfur. Subsequently, a variety of nucleosides were thiomethylated through this highly compatible protocol. Guanosin **3b** and purine riboside **3c** proceeded smoothly to afford the corresponding thiomethylation product on the 6-position of purine ring. Furthermore, methylamine-, ethylamine-, benzylamine-, and even cyclopropylamine- substituted adenosin were thiomethylated to afford **3d**, **3e**, **3f**, and **3g**, respectively.

Simazine **4a**,[23] which has a triazine-type structure, could be directly transformed to Simetryn **5a** in an 84% yield, which is another significant efficient and selective herbicide for paddy species (see Scheme 3).[24] Besides the thiomethyl group,

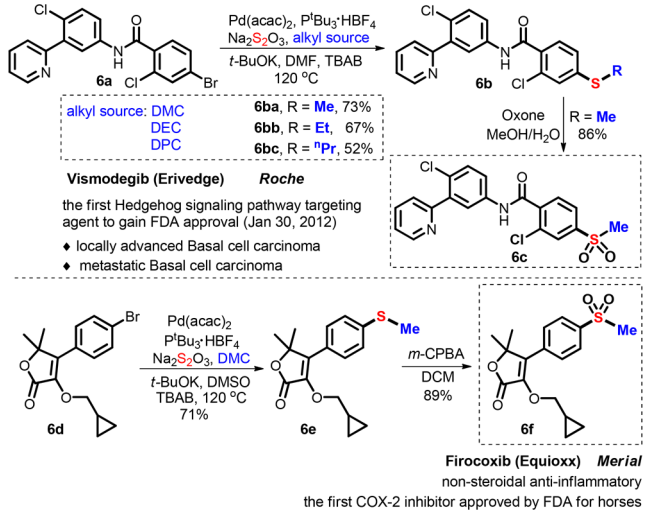
Scheme 3. Thiomethylation for Pesticides



thioethylated product **5b** could be afforded in a 76% yield when DMC was replaced by diethyl carbonate (DEC). Furthermore, sterically hindered dipropyl carbonate (DPC) could also be applied for thiopropylation, producing **5c** unhinderedly. These results indicated that this catalytic system could provide different types of thioalkyl functional groups by varying carbonates. Furthermore, diverse synthetic applications of pesticide were undertaken using a thiomethylated process. 6-Chloro-N^2-isopropyl-N^4-methyl-1,3,5-triazine-2,4-diamine, which was readily prepared from cyanuric chloride, was thiomethylated to furnish Desmetryn **5d** in a yield of 86%. Ametryn **5e**, which is widely used in corn, citrus, and sugar cane protection, was prepared from commercially available Atrazine in a yield of 86% via a one-step process. Prometryn **5f**,[25] which is a methylthio-*S*-triazine herbicide (registered as Caparol by Novartis Crop) that is used as protection to control annual broadleaf and grass weeds, could be efficiently synthesized in a yield of 91%. Terbutryn **5g**, Irgarol **5h**, Dimethametryn **5i**, and Methoprotryne **5j** were all afforded in excellent yields, which served as different types of protections for agriculture. Notably, higher isolated yield (93%) was achieved in the multigram-scale process for the synthesis of the Simetryn with a lower catalysis loading (2.5 mol %).

The current protocol also provided a synthetic shortcut for the marketed drug Vismodegib,[26] which is the first Hedgehog signaling pathway targeting agent, which gained FDA approval in Jan. 30, 2012. As shown in Scheme 4, Vismodegib **6c** could be

Scheme 4. Methylsulfide-Containing Pharmaceutical Synthesis



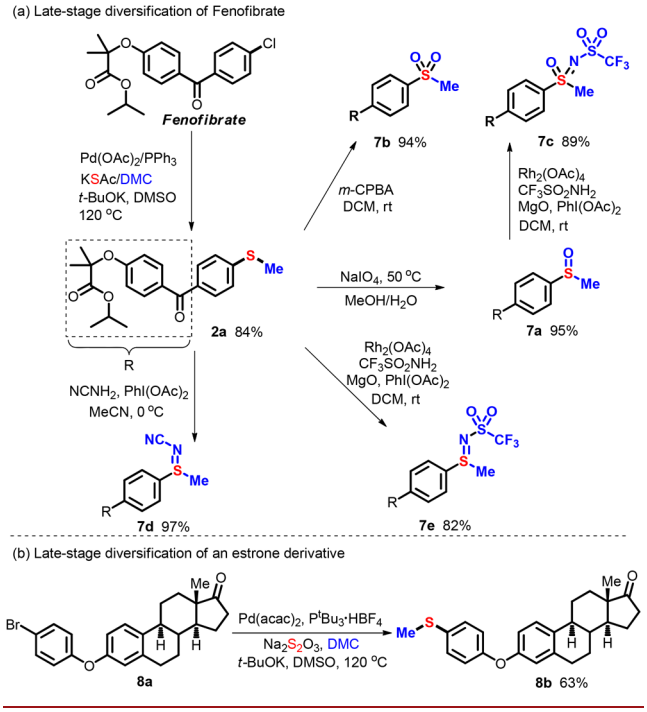
efficiently produced through highly selective thiomethylation of **6a** with multiple functional groups, with free amido linkage, followed by oxidation. **6a** can be smoothly furnished with different alkyl sources for the corresponding alkyl thioethers **6ba**–**6bc**, which displays potential for drug modification. In addition, a nonsteroidal anti-inflammatory drug Firocoxib (**6f**), which is the first COX-2 inhibitor approved by FDA for horses, was synthesized from aryl bromide **6d** through the current thiomethylation strategy, followed by oxidation (see Scheme 4).

The application of this thiomethylation strategy for late-stage diversification was demonstrated on Fenofibrate (marketed as Tricor by Abbott Laboratories), which serves as a cholesterol and triglycerides reducer in blood. The thiomethylated Fenofibrate **2a** can be afforded through this strategy in a yield of 84%, which is the key structure for diversified derivation. The organosulfur-based Fenofibrate with different oxidative states, providing methysulfinyl **7a**, methysulfonyl **7b**, imination product **7c**, *N*-cyano sulfilimines **7d**, and *N*-(trifluoromethyl)-sulfonyl sulfilimines **7e**, substantially assist the library establishment of organosulfur derivatives for drug discovery (see Scheme 5a).[27] Furthermore, late-stage modification of an estrone

DOI: 10.1021/acs.orglett.8b02677
Org. Lett. XXXX, XXX, XXX−XXX

derivative **8a** can also be efficiently achieved via the present strategy, providing the thiomethylation product **8b**.

Scheme 5. Late-Stage Diversification



In summary, this study provides an efficient and practical approach for thiomethylation with the combination of green inorganic sulfur source and methylation reagent, which surmounts the resistance of reductive elimination from palladium due to the strong coordination. Diverse functionalization of aryl methyl sulfides library is comprehensively established. The application on nucleosides demonstrates the compatibility with sensitive functional groups. A gram-scale reaction for the synthesis of pesticides shows a great potential for industrial process. The synthesis of Vismodegib and Firocoxib via the thiomethylation method can further manifest the practicability. Late-stage diversification for Fenofibrate and estrone expressed the multifunctional synthetic utility, which builds up a potential for drug discovery. Further study on the biological activities of these methylsulfides is underway in our research group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02677.

Experimental procedures, and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1517918−1517919 contain 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the NSFC (Nos. 21722202, 21672069, 21472050; Nos. 21871089 and 21502054 for M.W.), The National Key Research and Development Program of China (No. 2017YFD0200500), S&TCSM of Shanghai (Grant No. 18JC1415600), Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, and the National Program for Support of Top-Notch Young Professionals.

■ REFERENCES

(1) (a) Stiefel, E. I. Transition Metal Sulfur Chemistry: Biological and Industrial Significance and Key Trends. In *Transition Metal Sulfur Chemistry: Biological and Industrial Significance*; Stiefel, E. I., Matsumoto, K., Eds.; American Chemical Society: Washington, DC, 1996; Chapter 1, pp 2−38. (b) Fontecave, M.; Ollagnier-de-Choudens, S.; Mulliez, E. *Chem. Rev.* **2003**, *103*, 2149.

(2) (a) *Sulfur Compounds: Advances in Research and Application*; Acton, Q. A., Ed.; ScholarlyEditions: Atlanta, GA, 2012. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (c) Sulfur-containing pharmaceuticals can be found at the Njardarson research group: http://njardarson.lab.arizona.edu/.

(3) (a) Jacob, C.; Battaglia, E.; Burkholz, T.; Peng, D.; Bagrel, D.; Montenarh, M. *Chem. Res. Toxicol.* **2012**, *25*, 588. (b) Casida, J. E. *J. Agric. Food Chem.* **2016**, *64*, 4471. (c) Casida, J. E.; Durkin, K. A. *Chem. Res. Toxicol.* **2017**, *30*, 94.

(4) *Approved Drug Products with Therapeutic Evaluations (Orange Book)*, 33rd Edition; U.S. Department of Health and Human Services, U.S. Food and Drug Administration: Rockville, MD, 2013.

(5) Shiff, S. J.; Qiao, L.; Tsai, L. L.; Rigas, B. *J. Clin. Invest.* **1995**, *96*, 491.

(6) Barraclough, P.; Black, J. W.; Cambridge, D.; Collard, D.; Firmin, D.; Gerskowitch, V. P.; Glen, R. C.; Giles, H.; Hill, A. P. *J. Med. Chem.* **1990**, *33*, 2231.

(7) Giannetti, A. M.; Wong, H.; Dijkgraaf, G. J. P.; Dueber, E. C.; Ortwine, D. F.; Bravo, B. J.; Gould, S. E.; Plise, E. G.; Lum, B. L.; Malhi, V.; Graham, R. A. *J. Med. Chem.* **2011**, *54*, 2592.

(8) De Keijzer, J.; Mulder, A.; De Haas, P. E. W.; De Ru, A. H.; Heerkens, E. M.; Amaral, L.; Van Soolingen, D.; Van Veelen, P. A. *J. Proteome Res.* **2016**, *15*, 1776.

(9) Boldt, J.; Suttner, S. *Expert Opin. Pharmacother.* **2007**, *8*, 2135.

(10) Belley, M.; Gauthier, J. Y.; Grimm, E.; LeBlanc, Y.; Li, C.-S.; Therien, M.; Black, C.; Prasit, P.; Lau, C.-K.; Roy, P. U.S. Patent No. 5,981,576, Nov. 9, 1999.

(11) Sauer, J.; Boeck, W.; Von Hippel, L.; Burkhardt, W.; Rautenberg, S.; Arntz, D.; Hofen, W. U.S. Patent 5,852,219, Dec. 22, 1998.

(12) (a) Yamauchi, K.; Tanabe, T.; Kinoshita, M. *J. Org. Chem.* **1979**, *44*, 638. (b) Qiao, Q.; Dominique, R.; Sidduri, A.; Lou, J.; Goodnow, R. A., Jr *Synth. Commun.* **2010**, *40*, 3691. (c) Liu, C.; Szostak, M. *Chem. Commun.* **2018**, *54*, 2130.

(13) (a) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222. (b) Ma, D.; Geng, Q.; Zhang, H.; Jiang,

DOI: 10.1021/acs.orglett.8b02677
Org. Lett. XXXX, XXX, XXX−XXX

Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1291. (c) Liu, H.; Jiang, X. F. *Chem. - Asian J.* **2013**, *8*, 2546.
(14) DMSO is used as the source of MeS, mediated by a stoichiometric amount of metal salt; see: (a) Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304. (b) Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Sreedhar, B. *Tetrahedron* **2013**, *69*, 8276. (c) Ghosh, K.; Ranjit, S.; Mal, D. *Tetrahedron Lett.* **2015**, *56*, 5199.
(15) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007.
(16) (a) Xiao, X.; Xue, J.; Jiang, X. *Nat. Commun.* **2018**, *9*, 2191. (b) Xiao, X.; Feng, M.; Jiang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 14121. (c) Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2017**, *15*, 1942.
(17) Review: Tundo, P.; Musolino, M.; Aricò, F. *Green Chem.* **2018**, *20*, 28.
(18) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. *J. Med. Chem.* **2013**, *56*, 6007. (c) Nicolaou, K. C. *Chem. Biol.* **2014**, *21*, 1039.
(19) Miyamoto, L.; Watanabe, M.; Taoka, C.; Kono, M.; Tomida, Y.; Matsushita, T.; Kamiya, M.; Hattori, H.; Ishizawa, K.; Abe, S.; Nemoto, H.; Tsuchiya, K. *Mol. Pharmaceutics* **2013**, *10*, 2723.
(20) Qiao, Z.; Jiang, X. Potassium Thioacetate. In *Encyclopedia of Reagents for Organic Synthesis (e-EROS)*; John Wiley: New York, 2014, DOI: 10.1002/047084289X.rn01737.
(21) Liu, J.; Robins, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 5962.
(22) Duechler, M.; Leszczynska, G.; Sochacka, E.; Nawrot, B. *Cell. Mol. Life Sci.* **2016**, *73*, 3075.
(23) Regitano, J. B.; Koskinen, W. C.; Sadowsky, M. J. *J. Agric. Food Chem.* **2006**, *54*, 1373.
(24) Gianessi, L. P. Benefits of Triazine Herbicides. In *Triazine Herbicides: Risk Assessment*; Ballantine, L. G., McFarland, J. E., Eds.; ACS Symposium Series, Vol. *683*; American Chemical Society: Washington, DC, 1998, Chapter 1, pp 1−8.
(25) The structure is similar to **5f**; see: Avey, H. P.; Kennard, C. H. L.; Smith, G. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *41*, 938.
(26) Angelaud, R.; Reynolds, M.; Venkatramani, C.; Savage, S.; Trafelet, H.; Landmesser, T.; Demel, P.; Levis, M.; Ruha, O.; Rueckert, B.; Jaeggi, H. *Org. Process Res. Dev.* **2016**, *20*, 1509.
(27) Lücking, U. *Angew. Chem., Int. Ed.* **2013**, *52*, 9399.

DOI: 10.1021/acs.orglett.8b02677
Org. Lett. XXXX, XXX, XXX−XXX