One-Step Synthesis of Sulfonamides from *N*-Tosylhydrazones

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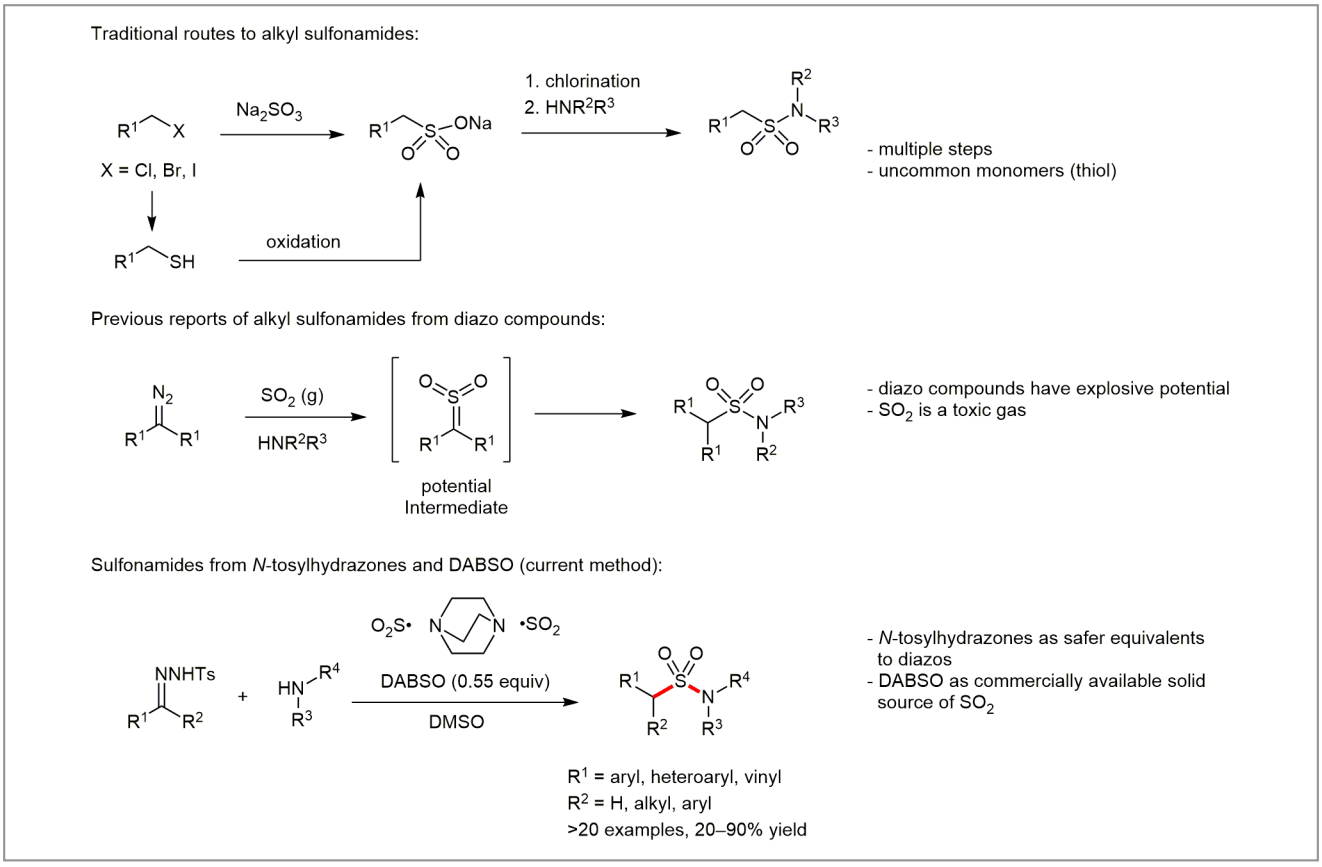
Since the discovery of the sulfa antibiotics in the 1930s, the sulfonamide motif has been a prevalent pharmacophore found in many medicines and drug candidates. Thus, sulfonamide formation is commonly sought after to explore structure–activity relationships (SAR) during drug discovery efforts. While traditional syntheses of sulfonamides are straightforward from sulfonyl chlorides and amines, several steps are generally required to prepare the necessary sulfonyl chloride. To address the limitations from these early methodologies, recent work from Pfizer and other groups led to the development of convenient one-pot methods to obtain sulfonamides starting from a large pool of readily available reactants such as (hetero)aryl/alkyl halides or (hetero)arylboronic acids and amines (see the original article for references). One particular project called for the synthesis of a variety of alkyl sulfonamides. Following from their previous work in the Pfizer laboratories, Dr. Andy Tsai and his co-workers at Pfizer Worldwide Medicinal Chemistry (Groton, USA) sought to develop novel methods for accessing alkyl sulfonamides from other commonly encountered starting materials.

"In thinking about a new method to make alkyl sulfonamides, several features were important," said Dr. Tsai. "First is that the reaction leverages commonly encountered reactants, which is important for parallel synthesis application and to support rapid SAR exploration." Dr. Tsai continued: "Operational simplicity is also of paramount importance, especially in the context of parallel synthesis setting. With these factors in mind, of particular interest to us were decades old reports that showed alkyl sulfonamides could be obtained from alkyl diazo compounds, SO_2 (gas), and amines." These



Scheme 1

reports approached the reaction largely as a curiosity: the mechanism was explored but their synthetic value was not, which may not be surprising as diazo species are explosive and SO_2 is a toxic gas. However, in the intervening decades since these reports, *N*-tosylhydrazones have been appreciated as safer equivalents to diazo compounds and DABSO {1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct} has been developed as a convenient solid source of SO_2 gas. "With the consideration that *N*-tosylhydrazones are simply obtained from condensation using commonly encountered ketones and aldehydes, we reckoned that the reaction held the potential of a novel route to sulfonamides," said Dr. Tsai.

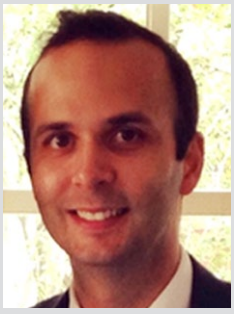
Preliminary experiments showed that mixing the *N*-tosylhydrazone, DABSO, and an amine in DMSO provided the desired sulfonamide. After some optimization, the substrate scope was defined. "Our current work is to extend the scope to include non-aromatic *N*-tosylhydrazones," said Dr. Tsai. "To guide us to this goal, we hope to be able to use react-IR and in-situ NMR to identify key intermediates in the reaction to help elucidate the mechanism."

Dr. Tsai concluded: "In summary, this method provides a novel route to sulfonamides from aldehydes and ketones (via their condensation with *N*-tosylhydrazide). The simple reaction setup and ready availability of diverse building blocks provide a basis for compound libraries to explore SAR in future drug discovery efforts."

About the authors

Dr. A. Tsai

Andy Tsai graduated with a B.S. in chemistry from University of Michigan (USA). Subsequently, he studied under the direction of Professors Jonathan Ellman and Robert Bergman at the University of California, Berkeley (USA) in the area of C–H activation. Upon receiving his Ph.D in 2011, he moved down to the Scripps Research Institute in Jupiter, Florida (USA) where he worked as a postdoctoral associate with Professor William Roush. He is currently a medicinal chemist at Pfizer.



Dr. J. Curto

John Curto was born and raised in western Massachusetts (USA). He obtained his undergraduate degree at the College of the Holy Cross in Worcester, MA (USA), where he was first introduced to research while working for Professor Kevin Quinn on the synthesis of small natural products. In 2014, John graduated from the University of Pennsylvania (USA) with a Ph.D. under the guidance of Professor Marisa Kozlowski on the asymmetric synthesis of α,α-disubstituted α-amino acids and studies on the palladium-catalyzed C(sp^3)–H activation of alkyl arenes. John and his wife Barb currently live in Connecticut where John has begun his career as a medicinal chemist.

Dr. B. N. Rocke

Benjamin N. Rocke was born and raised near Peoria, IL (USA). In 2004, he received a B.S. in chemistry from the University of Illinois at Urbana-Champaign (USA), where his research in the lab of Professor Gregory S. Girolami resulted in an award-winning thesis. Since then, he has been employed by Pfizer in Groton, CT (USA). His work has contributed to the advancement of several molecular entities as clinical candidates for the treatment of type II diabetes or cardiovascular disorders. Ben enjoys tuning and repairing pianos in his spare time, as well as spending time with his family.

Dr. A.-M. Dechert Schmitt

Anne-Marie Dechert Schmitt obtained her B.S. degree in chemistry from the University of Georgia (USA), and completed undergraduate research under the direction of Professor Tim Dore. From there, Anne-Marie moved to the University of North Carolina (USA) to complete her graduate work. Her work focused on the synthesis of polyketide natural products under the tutelage of Professor

Michael Crimmins. She joined Professor Michael Krische as a postdoctoral researcher in 2011, and studied Ir-catalyzed C–C bond-forming reactions. She currently works at Pfizer in Groton, CT (USA) as a senior scientist in the CVMET group.

Dr. G. Ingle

Gajendra Ingle was born in India and after completing his undergraduate degree, he moved to Utah State University in Logan, UT (USA) for his Master's degree in chemistry. In 2007, Gajendra joined Professor Jon Antilla's laboratory at University of South Florida, Tampa, FL (USA) for graduate studies, where he investigated chiral phosphoric acid/metal phosphate catalyzed transformations of imines and epoxides. As a postdoctoral scholar in Professor Dean Toste's laboratory at University of California, Berkeley (USA), he worked on the chiral phosphate anion catalyzed macrocyclization reaction of malonate-appended diazonium salts. He joined Pfizer in December 2014, and is currently working as a Senior Scientist in CVMET in Groton, CT (USA).

Dr. V. Mascitti

Vincent Mascitti received his diploma in chemical engineering from the ECPM (Strasbourg, France). He then completed his Ph.D. with Professor Stephen Hanessian (University of Montreal, Canada) on the total synthesis of natural products bearing deoxypropionate motifs (e.g., doliculide and borrelidin), and the synthesis of bioactive oligosaccharides. He did his postdoctoral studies in the laboratories of Professor E. J. Corey where he completed the first total synthesis of the ladderane-containing natural product pentacycloanammoxic acid. Vincent joined Pfizer in 2006, where as a medicinal chemist in the CVMED chemistry department he contributed to various diabetes- and obesity-related projects. In particular, Vincent was the driving force behind the design and synthesis of SGLT2 inhibitor Ertugliflozin (PF-04971729), a clinical candidate currently in development and being evaluated for type II diabetes treatment. Vincent is the (co)author of over 40 publications and patent applications. He is currently a Senior Director at Pfizer in the CVMET medicinal chemistry department.

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