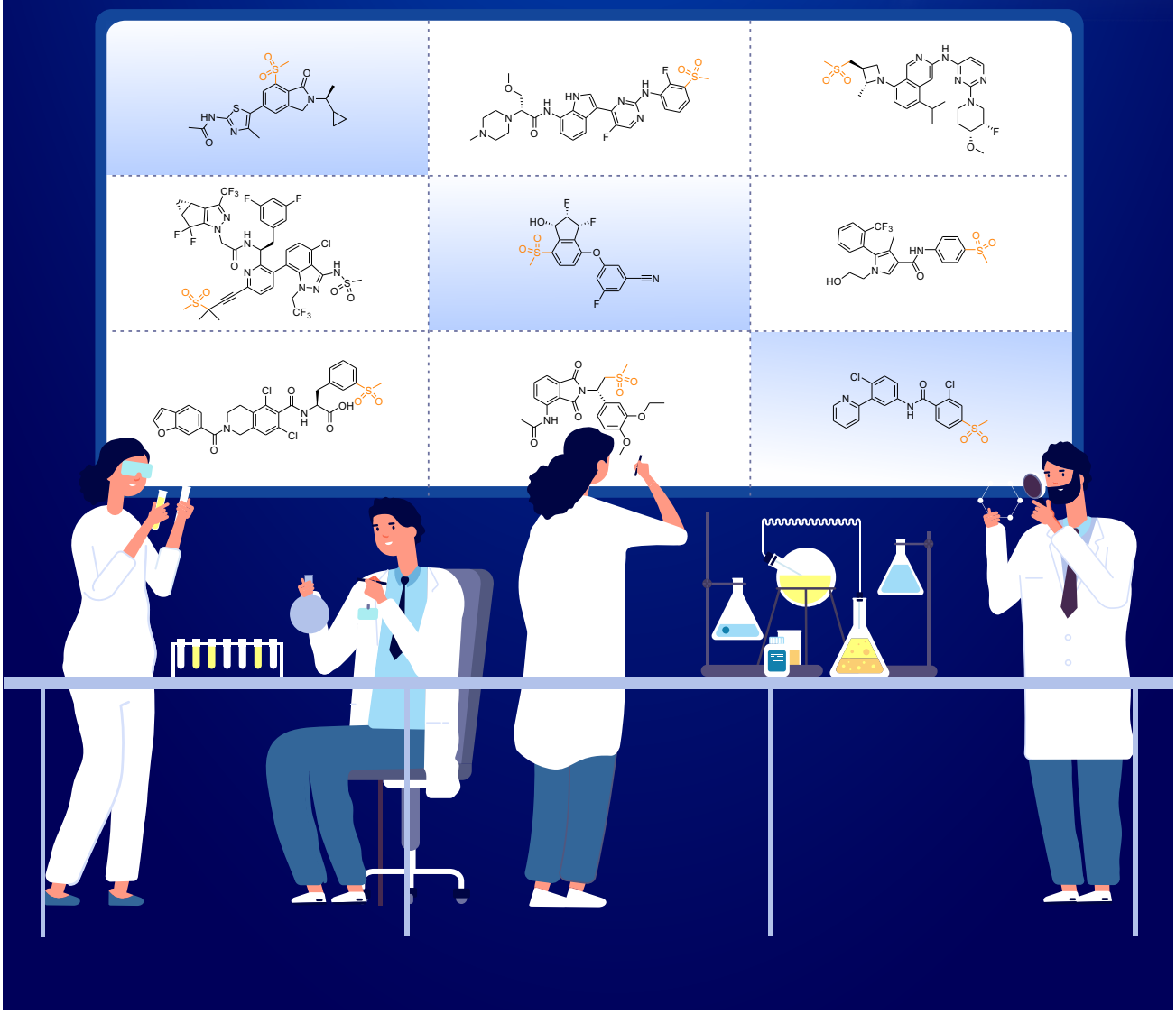
PharmaBlock

SCIENTIFIC INSIGHTS

Application of Methylsulfone in Drug Discovery



www.pharmablock.com

General Introduction of Methylsulfone

Currently, more than 150 FDA-approved sulfur S(**VI**)-containing drugs, mostly bearing a sulfonyl functional group, are available in the market to treat various types of diseases[1]. They constitute an important class of drugs used as anti-inflammatory, antibacterial, antifungal, antitumor, alzheimer diseases, or antiviral agents. The application of the sulfonyl functional group is widely practiced in medicinal chemistry. This mini-review mainly focuses on the synthesis of sulfones and related building block products.

Methyl sulfone, often found in the structures of marketed drugs and (pre-) clinical candidates[2-7] (**Figure 1**), is an important motif in medicinal chemistry because of its unique drug-likeness features. It has a powerful electron-withdrawing effect, which can affect many physicochemical properties accordingly, such as the basicity-lowering effect[8]. It can significantly reduce the lipophilicity of the molecule to improve the solubility of the molecule, and slow down the metabolism of the molecule. It's also very stable against hydrolysis, and resistant to reduction in sulfur. Methylsulfone has already become one of the top choices for medicinal chemists to incorporate in the new drug design.

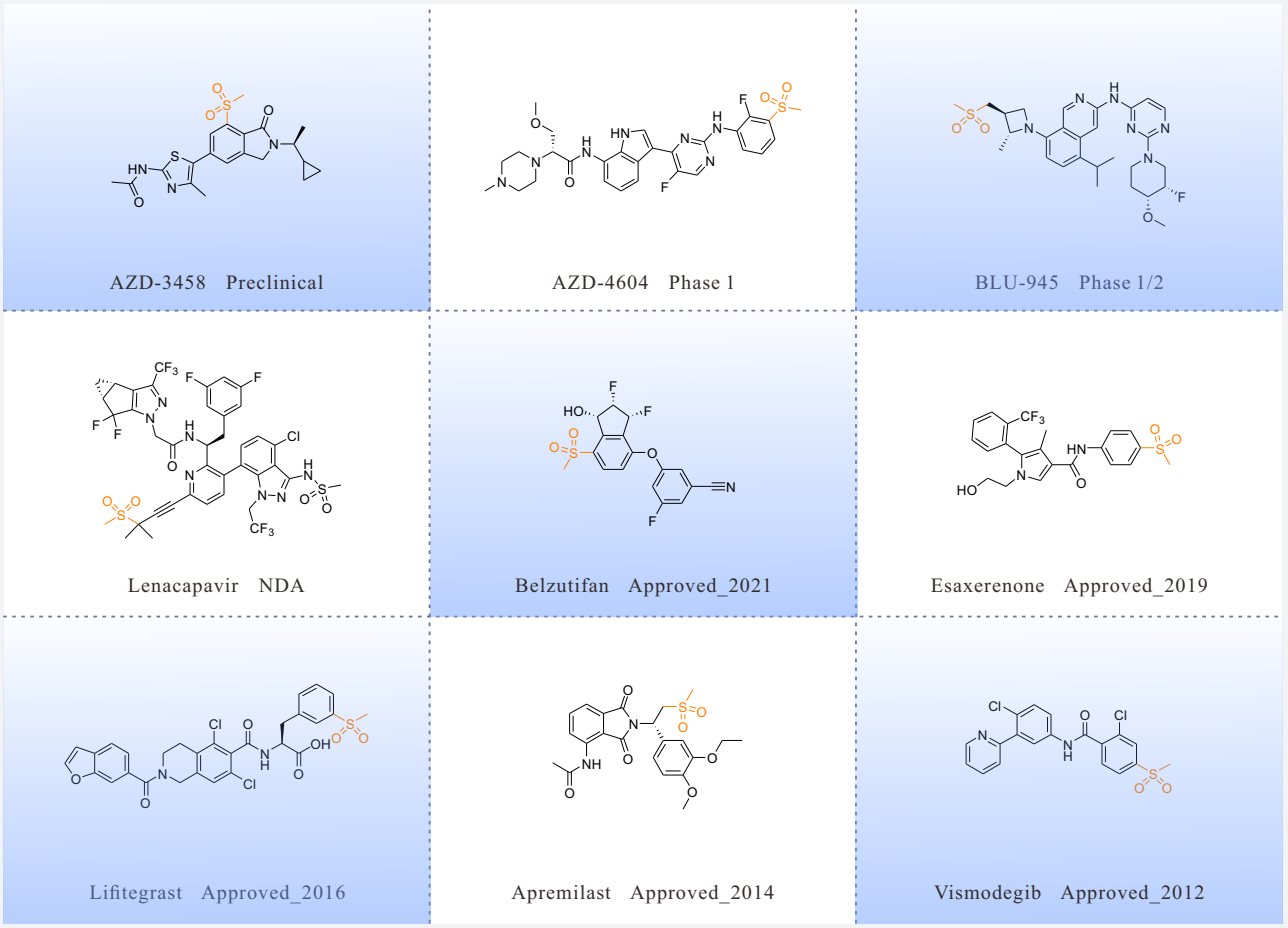
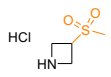
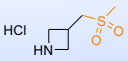
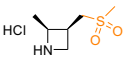
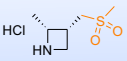
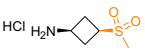
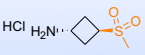
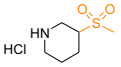
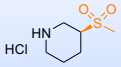
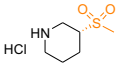
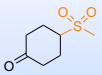
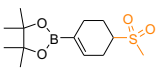
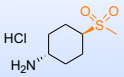
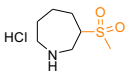
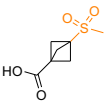
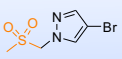
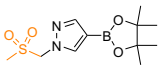
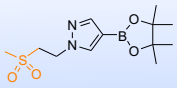
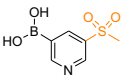
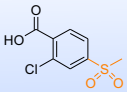
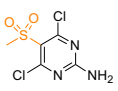
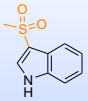
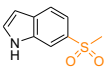
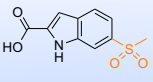
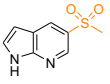
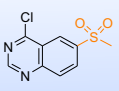


Figure 1. Approved drugs and (pre-) clinical candidates containing methylsulfone

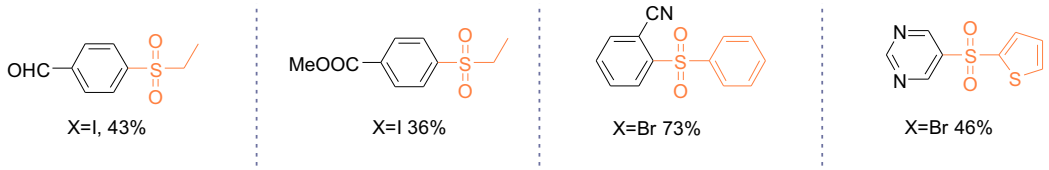
Building Blocks Containing Methylsulfone

PharmaBlock has conducted a systematic study on marketed, clinical, and preclinical drug structures containing methylsulfone (**Figure 1**). Our chemists stay updated on the latest researches to design and synthesize new building blocks containing methylsulfone to support exploration of structure-activity relationship (SAR) and structure-property relationship (SPR). We offer >1000 unique building blocks containing methylsulfone on from gram to kilogram scale in stock.

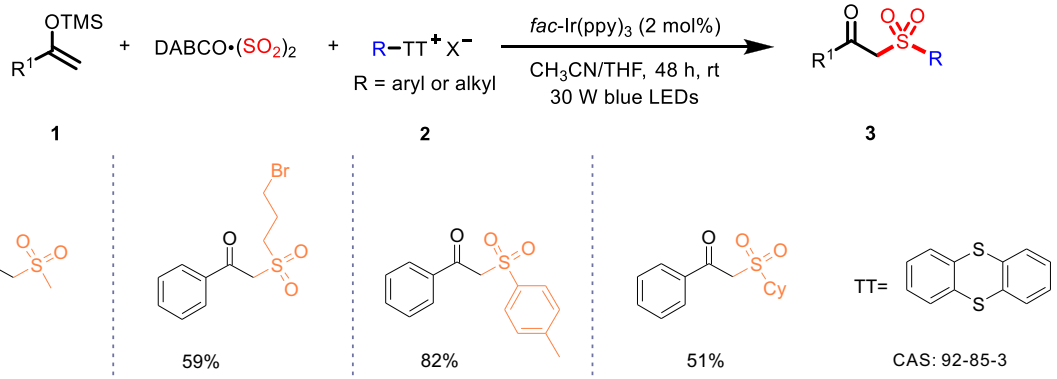
BUILDING BLOCKS						
						
	PB00234-01 1400764-60-4	PB01237-1 1820683-31-5	PBZL260-1 2725774-17-2	PBZL261-1 2725774-19-4	PBN20120741-01 1408074-56-5	PBN20120740-01 1408075-97-7
						
PB00487 433980-62-2	PB00833 1234567-84-1	PB00834 290328-57-3	PB00310 290328-55-1	PB00835-01 1378304-65-4	PB00837-01 1946010-89-4	PB00836-1 1946010-93-0
						
PBWB8219 862129-72-4	PBS1407160 862129-71-3	PBLG444-1 2173637-90-4	PBTEN15557-1 1788990-57-7	PB93847 1886967-22-1	PBZ2638 1886967-73-2	PBTQ5803 1249197-58-7
						
PBLG120 2109226-54-0	PBXA1136 1799792-00-9	PB06320 1282530-99-7	PBLJ2798 1339892-52-2	PBZ5200 49651-55-0	PBU8642 1559062-17-7	PBEB10240 913836-01-8
						
PB03868 53250-83-2	PBU0821 78744-34-0	PBLJ2328 582321-06-0	PBXJ685 467461-40-1	PBU2090 383132-63-6	PB01425 1036383-51-3	PBS59043 1256955-37-9

Sulfone Chemistry

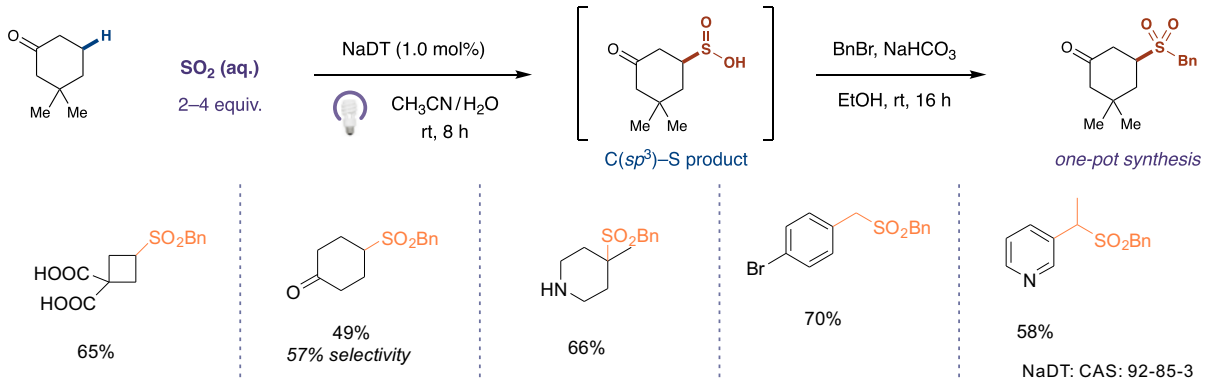
1) Synthesis of sulfone via photocatalytic reaction:



Ref. Sulfonylation of Aryl Halides by Visible Light/Copper Catalysis *Org. Lett.* **2021**, *23*, 3663−3668

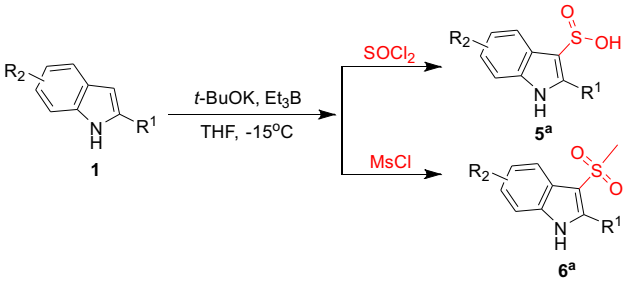


Ref. Photoredox-Catalyzed α-Sulfonylation of Ketones from Sulfur Dioxide and Thianthrenium Salts *Org. Lett.* **2022**, *24*, 2955−2960

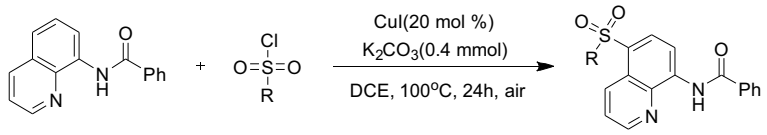


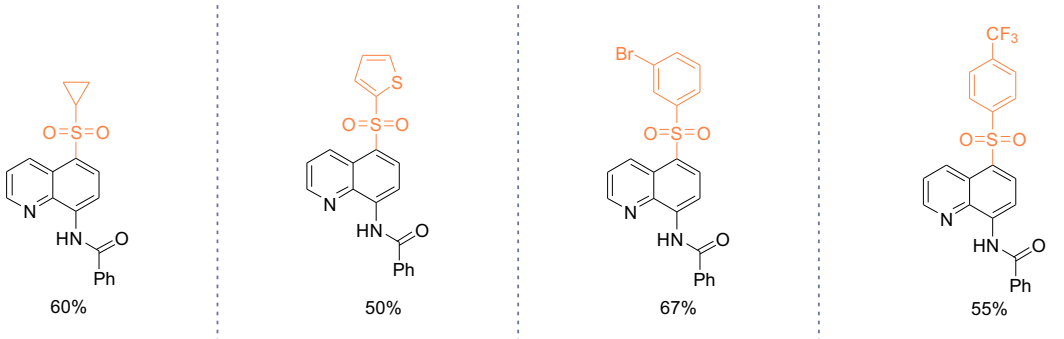
Ref. Decatungstate-Catalyzed C (sp3)−H Sulfinylation: Rapid Access to Diverse Organosulfur Functionality J. *Am. Chem. Soc.* **2021**, *143*, 9737−9743

2) Synthesis of sulfone via sulfonyl chloride:



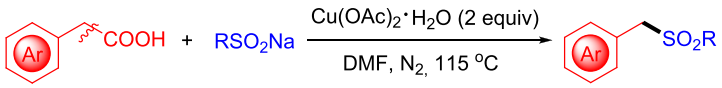
Ref. Collective Synthesis of 3-Acylindoles, Indole-3-carboxylic Esters, Indole-3-sulfinic Acids, and 3-(Methylsulfonyl) indoles from Free (N−H) Indoles via Common N-Indolyl Triethylborate *Org. Lett.* **2016**, *18*, 3918−3921

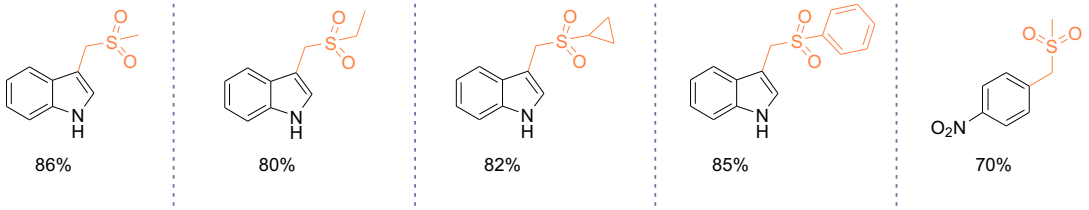




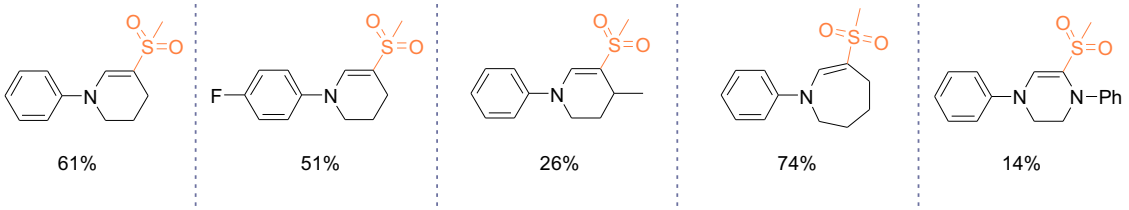
Ref. Copper(I)-Catalyzed Sulfonylation of 8-Aminoquinoline Amides with Sulfonyl Chlorides in Air *Org. Lett.* **2015**, *17*, 6086−6089

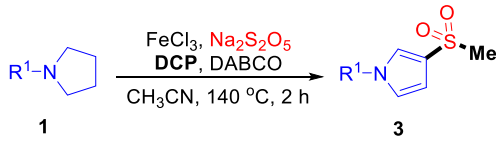
3) Synthesis of sulfone via transition metal catalyzed reaction:

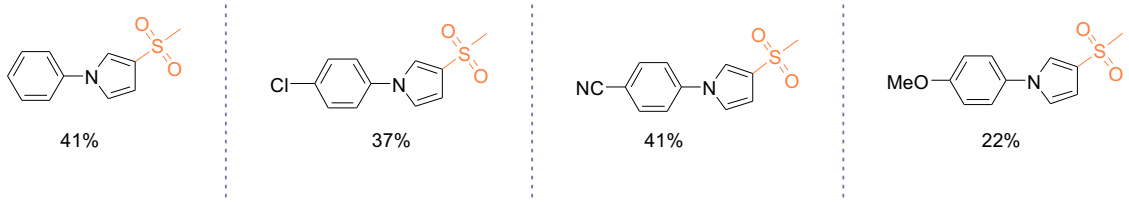




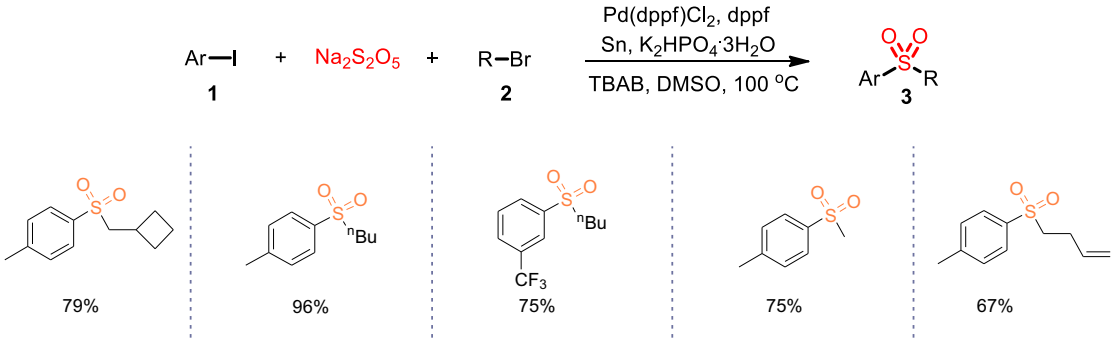
Ref. Copper-Mediated Decarboxylative Sulfonylation of Arylacetic Acids with Sodium Sulfinates *Org. Lett.* **2020**, *22*, 7164−7168



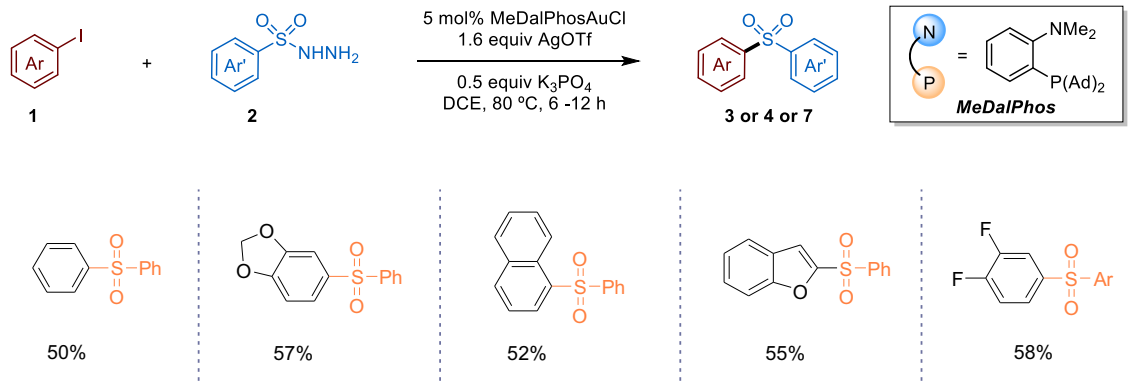




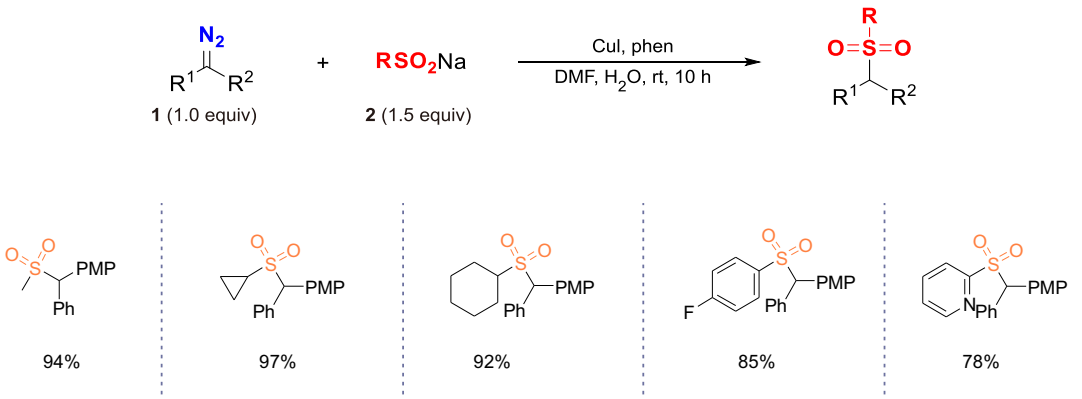
Ref. Synthesis of β-Methylsulfonylated N-Heterocycles from Saturated Cyclic Amines with the Insertion of Sulfur Dioxide *J. Org. Chem.* **2020**, *85*, 15600−15609



Ref. Multicomponent Reductive Cross-Coupling of an Inorganic Sulfur Dioxide Surrogate: Straightforward Construction of Diversely Functionalized Sulfones *Angew. Chem. Int. Ed.* **2020**, *59*,1346-1353



Ref. Ligand-Enabled Gold-Catalyzed C(sp2)−S Cross-Coupling Reactions *Org. Lett.* **2022**, *24*, 4459−4463

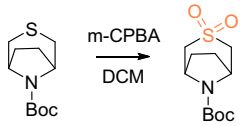


Ref. Copper-Mediated Cross-Coupling of Diazo Compounds with Sulfinates *Org. Lett.* **2021**, *23*, 6919−6924

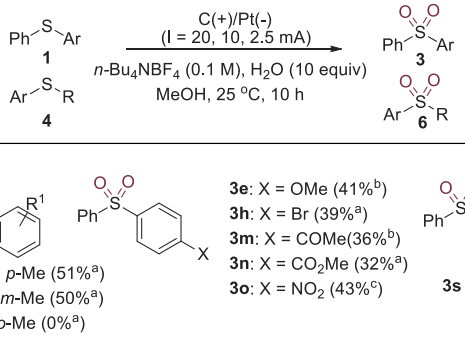
4) Synthesis of sulfone by oxidation of thioether:

Oxidation reagents: m-CPBA, CrO_3, oxone, H_5IO_6 /CrO_3, H_2O_2/$NaWO_4$ *etc.*

For example:

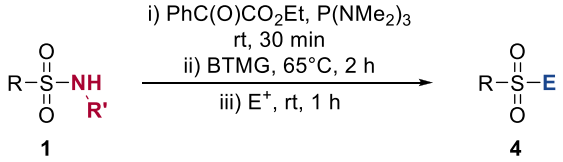


There have some research on the synthesis of sulfoxide or sulfoxide via Electrochemical Oxidation of Sulfides

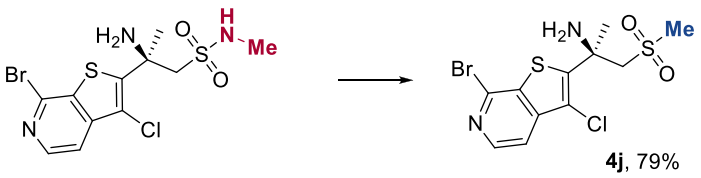


Ref. Sulfoxide and Sulfone Synthesis via Electrochemical Oxidation of Sulfides *J. Org. Chem.* **2021**, *86*, 13790−13799

5) Other methods:



For example:



Ref. Reductive Cleavage of Secondary Sulfonamides: Converting Terminal Functional Groups into Versatile Synthetic Handles *J. Am. Chem. Soc.* **2019**, *141*, 18416−18420

PharmaBlock has capabilities of conducting photocatalytic reactions, including flow photocatalytic reactions-and electrochemical reactions.

References

[1] Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review. Chuang Zhao *et al*. *Eur. J. Med. Chem.* **2019**, *162*, 679-734.

[2] Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. Bester *et al*. *Science* **2020**, *370*, 360-364.

[3] Clinical targeting of HIV capsid protein with a long-acting small molecule. Link JO *et al*. *Nature* **2020**, *3*, 45-51.

[4]3-[(1S,2S,3R)-2,3-Difluoro-1-hydroxy-7-methylsulfonylindan-4-yl]oxy-5 fluorobenzo nitrile (PT2977), a Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitor for the Treatment of Clear Cell Renal Cell Carcinoma. Rui Xu *et al*. *J. Med. Chem.* **2019**, *62*, 6876-6893.

[5] Discovery and Development of Potent LFA-1/ICAM-1 Antagonist SAR 1118 as an Ophthalmic Solution for Treating Dry Eye. Min Zhong *et al*. *ACS Med. Chem. Lett.* **2012**, *3*, 203–206.

[6] Discovery of highly isoform selective orally bioavailable phosphoinositide 3-kinase (PI3K)-γ inhibitors. Pemberton, N *et al*. *J. Med. Chem.* **2018**, *61*, 5435-5441.

[7] Discovery of BLU-945, a Reversible, Potent, and Wild-Type-Sparing Next-Generation EGFR Mutant Inhibitor for Treatment-Resistant Non-Small-Cell Lung Cancer. Meredith S. Eno *et al*. *J. Med. Chem.* **2022**, DOI:10.1021/acs.jmedchem.2c00704.

[8] Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities. K. Müller *et al*. *ChemMedChem* **2007**, *2*, 285-287.

About Author

Dr. Lisha Wang
Director of CADD

Ph.D., Shanghai Institute of Organic Chemistry Chinese Academy
Postdoc in Aaron Diamond AIDS Research Center (ADARC), the Rockefeller University,
Research Investigator & Project leadership member, CADD, Roche R&D Center (China)
Principal Scientist, CADD, Roche Basel (Switzerland)
60 publications including 40 patents

Jin Li
Senior Director

10+ years' experience in organic chemistry and 3+ year's experience in medicinal chemistry
10+ patents and papers published
Inventor of 2 clinical candidates

Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): +1 (877) 878-5226 Tel (CA): +1 (267) 649-7271
Email: salesusa@pharmablock.com

Find out more at www.pharmablock.com

Official Website | Product Search | Wechat | LinkedIn

Feb. 2023

ナミキ商事株式会社

本社
〒160-0022　東京都新宿区新宿5-5-3　建成新宿ビル
TEL：03-3354-4026　　FAX：03-3352-2196

大阪支店
〒541-0044　大阪市中央区伏見町2-5-7　岡田伏見町ビル
TEL：06-6231-5444　　FAX：06-6233-6540

E-mail：info@namiki-s.co.jp
URL：http://www.namiki-s.co.jp