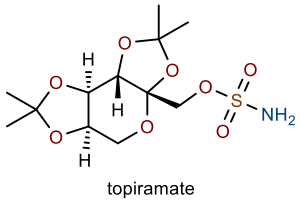
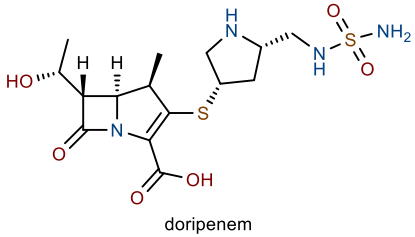
Sulfamoylation Reagents

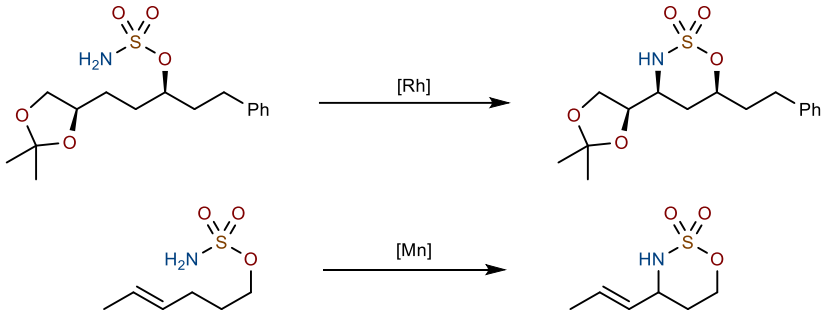
Background

Sulfamates and sulfamides are useful moieties in pharmaceuticals



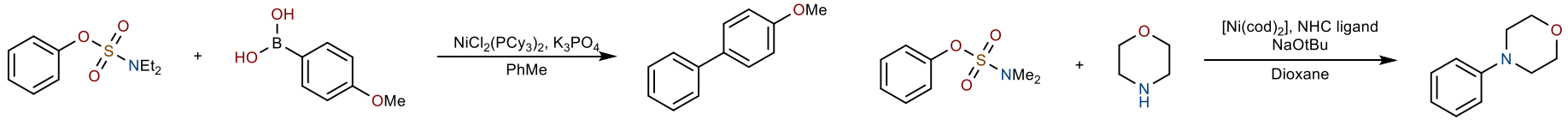


They have also found use in C-H activation chemistry as nitrene precursors



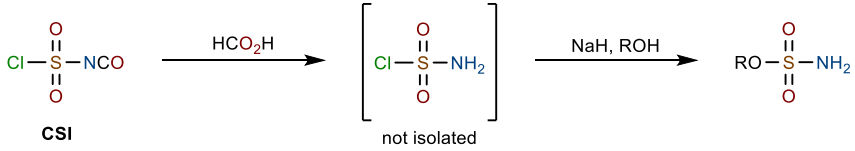
Du Bois, J. *Angew. Chem. Int. Ed.* **2004**, 43 (33), 4349–4352. https://doi.org/10.1002/anie.200460791; White, M. C. *Nature Chem.* **2015**, 7 (12), 987–994. https://doi.org/10.1038/nchem.2366

Cross coupling of aryl sulfamates with amines or boronic acids is possible with nickel catalysis



Garg, N. K. *J. Am. Chem. Soc.* **2009**, 131 (49), 17748–17749. https://doi.org/10.1021/ja906477r; Garg, N. K. *Angew. Chem. Int. Ed.* **2011**, 50 (9), 2171–2173. https://doi.org/10.1002/anie.201007325

Classical Sulfamoylation – *In situ* Generation of sulfamoyl chloride



Potential issues:

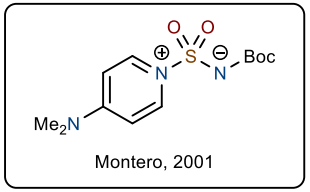
- Must generate sulfamoyl chloride every time
- Generally, excess (2-4 eq) of chlorosulfonyl isocyanate is used
- Low selectivity for primary vs. secondary alcohols
- Challenges upon scaleup due to violent gas evolution

Appel, R. *Chemische Berichte* **1958**, 91 (6), 1339–1341. https://doi.org/10.1002/cber.19580910633

Fun fact: developed by Rolf Appel – the same as the eponymous reaction for converting alcohols to alkyl halides

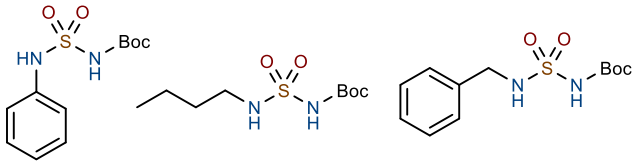
Sulfamoylation Reagents

Burgess-type Inner Salt Reagents

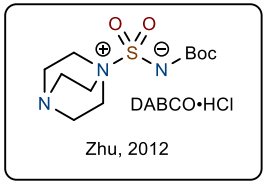


Montero, 2001

- Prepared by addition of tBuOH followed by DMAP to CSI
- Used for the sulfamoylation of amines and anilines to give sulfamides (ROH not reactive)
- Bench stable

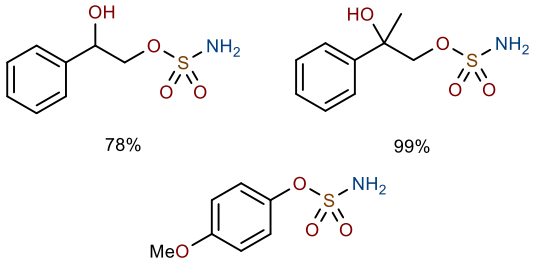


Montero, J.-L. *Org. Lett.* **2001**, 3 (14), 2241–2243. https://doi.org/10.1021/ol0161312

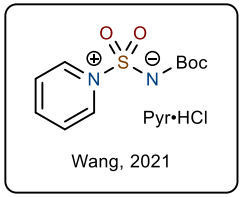


Zhu, 2012

- Prepared by addition of tBuOH followed by DABCO to CSI
- Reactive towards amines, anilines, alcohols, and phenols
- Catalytic HCl enhances reaction rate of sulfamoylation
- Bench stable

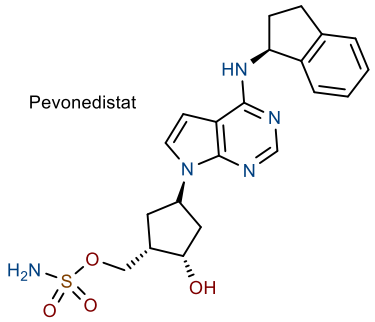


Zhu, L. *Org. Lett.* **2012**, 14 (10), 2626–2629. https://doi.org/10.1021/ol3009683



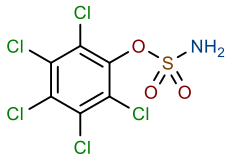
Wang, 2021

- Prepared by addition of tBuOH followed by pyridine to CSI
- Similar reactivity as Zhu's reagent, but improved solubility
- Bench stable



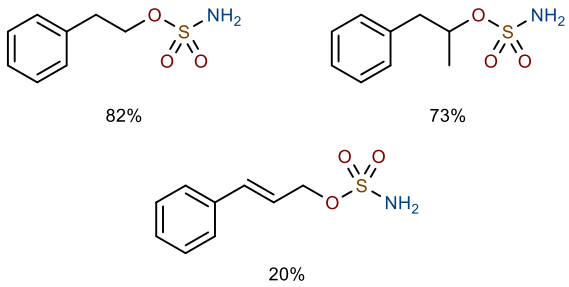
Wang, D.-Y. *Org. Lett.* **2021**, 23 (7), 2595–2599. https://doi.org/10.1021/acs.orglett.1c00504

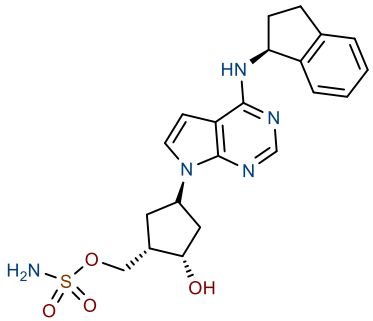
Activated Aryl Sulfamates



Miller, 2020

- Prepared by trapping sulfamoyl chloride with pentafluorophenol
- Catalytic NMI allows for facile sulfamate formation
- Bench stable



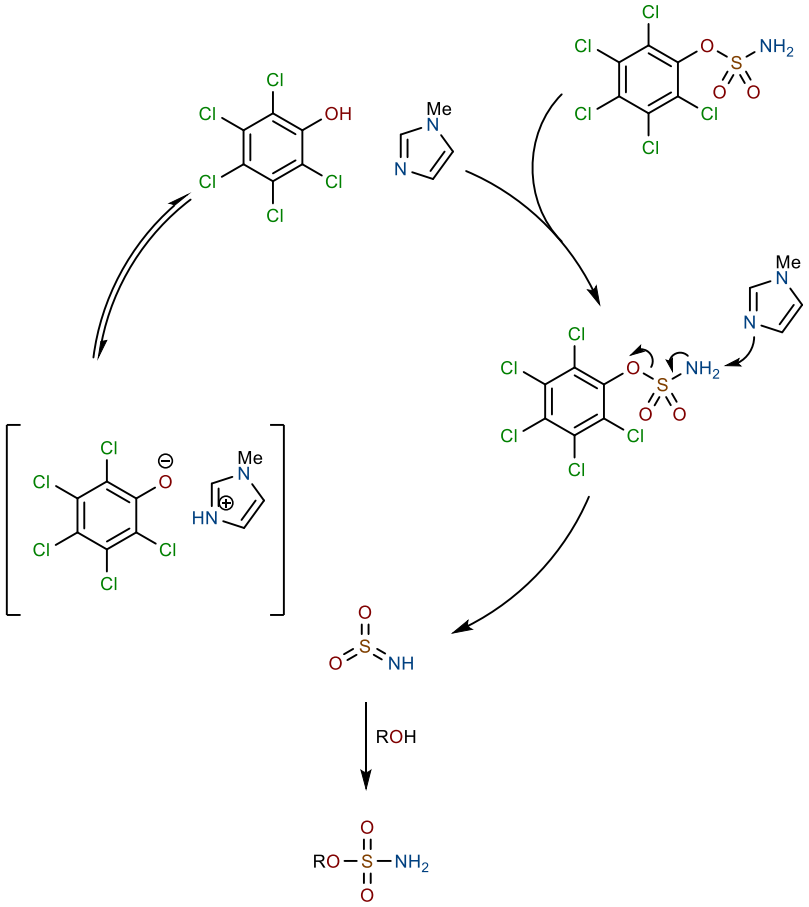


Miller, S. J. *Org. Lett.* **2020**, 22 (1), 168–174. https://doi.org/10.1021/acs.orglett.9b04119

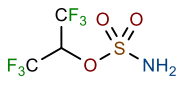
Sulfamoylation Reagents

Activated Aryl Sulfamates Continued

Proposed mechanism involves the formation of an aza-sulfene, which is trapped by the alcohol or amine nucleophile

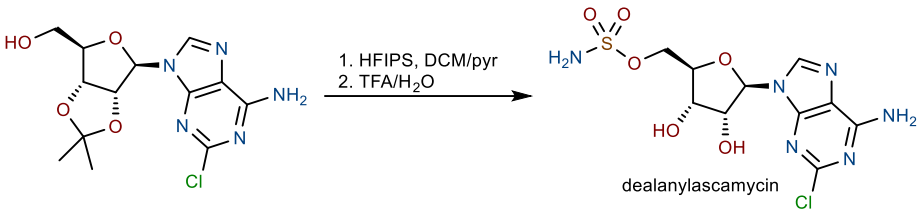


Hexafluoroisopropanol sulfamate (HFIPS)



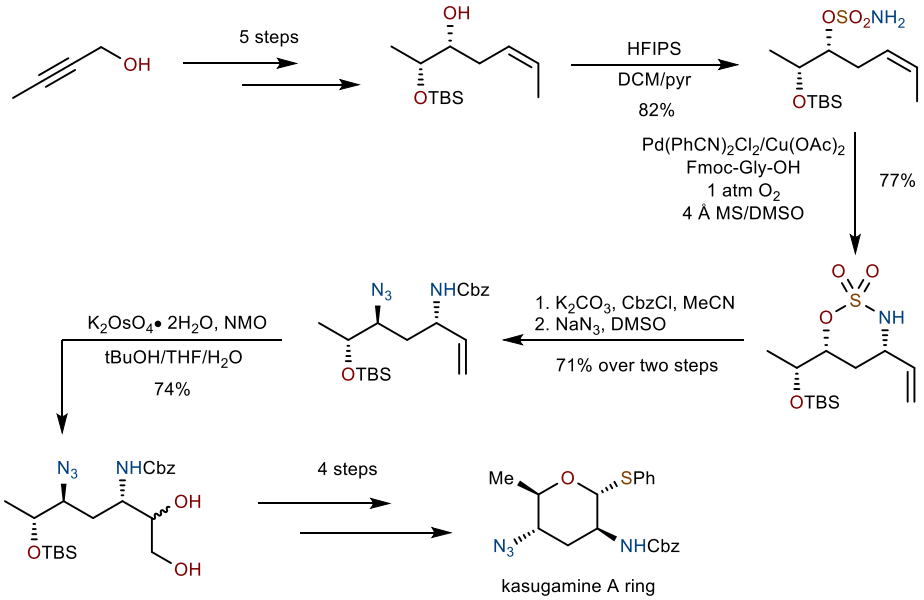
Magolan, 2021

- Prepared by trapping sulfamoyl chloride with HFIP
- HFIP byproduct easy to remove by evaporation after sulfamate/sulfamide formation
- Reactive towards amines, alcohols, anilines, and phenols
- Bench stable



Magolan, J. *Org. Lett.* **2021**, 23 (9), 3373–3378. https://doi.org/10.1021/acs.orglett.1c00855

Example in Total Synthesis – (+)-Kasugamycin



Sathyamoorthi, S. *Org. Lett.* **2024**, 26 (26), 5463–5466. https://doi.org/10.1021/acs.orglett.4c01726