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New Synthesis of β-Sultams from Pentafluorophenyl Sulfonates

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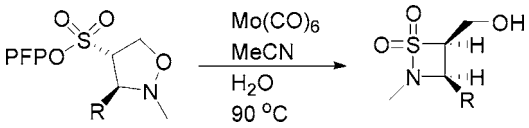
ABSTRACT



A stereoselective one-pot synthesis of substituted 1,2-thiazetidine 1,1-dioxides (β-sultams) has been achieved from heterocyclic pentafluorophenyl (PFP) sulfonates. Mild N–O bond cleavage of isoxazolidines followed by intramolecular cyclization of the amine onto the PFP demonstrates the potential utility for using the PFP sulfonate as a valuable precursor to sulfonamides.

The sulfonamide moiety has long been established as displaying biological activity and as such is widely found in molecules of medicinal interest, particularly antibacterial agents.[1] Sulfonamides are able to act as carbonic anhydrase inhibitors and have been used clinically for over 50 years in the treatment of glaucoma, epilepsy, and heart failure.[2] Furthermore, sultams, the cyclic analogues of sulfonamides, have revealed a wide array of biological activity in areas such as nonsteroidal antiinflammatory agents.[3]

The speed with which bacteria and viruses are able to mutate means that there is a constant battle to obtain new bioactive compounds for drug delivery. An example is the emergence of penicillin-resistant bacteria. Penicillin contains a bicyclic β-lactam system, which acylates nucleophilic residues in a wide range of bacterial and mammalian enzymes. Acylation of the serine residue prevents the final transpeptidation of the peptidoglycan layer, disrupting the cell wall synthesis and ultimately leading to cell death.[4] One method, in which bacteria have become resistant, is through the production of β-lactamase. β-Lactamases hydrolyze the β-lactam ring, thus destroying the molecule's antibacterial properties. Consequently, there is an ever increasing requirement for the development of new bioactive pharmacophores to overcome resistance, particularly associated with β-lactamases. β-Sultams are the sulfur analogues of β-lactams and have recently been shown to inhibit serine β-lactamases[5] as well as the serine protease elastase.[6] Furthermore, it has been determined that inhibition occurs via irreversible sulfonylation of the active site serine.

The obvious potency of the sulfonamide (cyclic and acyclic) motif and the requirement for new, mild, and generic methods led us to investigate alternative syntheses for sulfonamides, which negate the use of toxic, nonstable precursors. We have previously reported the synthesis of a wide variety of sulfonamides utilizing the surprisingly stable pentafluorophenol (PFP) vinyl sulfonate moiety.[7] The PFP vinyl sulfonate moiety undergoes both radical[7b,c] and 1,3-dipolar cycloaddition chemistry,[7d] the latter resulting in the regio- and stereoselective formation of isoxazolidines.

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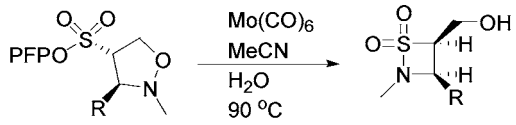
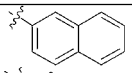
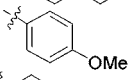
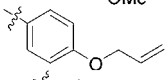
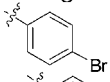
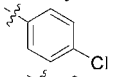
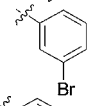
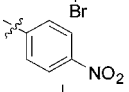
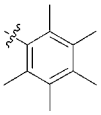
Table 1. $Mo(CO)_6$ Reductive Cleavage of Isoxazolidines to Their Corresponding β-Sultams



entry	R	yield %
1		58
2		53
3		52
4		50
5		47
6		37
7		37
8		27
9		27
10		26
11		0
12		0

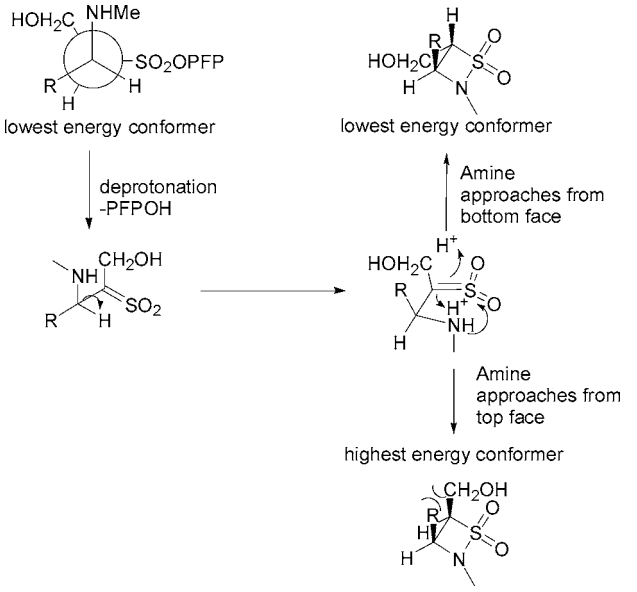
Encouraged by these findings, we sought alternative routes to promote further functional group interconversion. Having thoroughly studied the formation of acyclic sulfonamides, we became intrigued by the possibility of forming sultams (cyclic sulfonamides) from these intermediates. We, herein, report a new strategy for the synthesis of β-sultams via selective ring cleavage of the N−O bond of isoxazolidines and subsequent displacement of pentafluorophenol.

There are several methods reported for the reductive cleavage of isoxazolidines into the corresponding amino alcohols, including Pd/C, Zn/H^+, hydrogenation over Raney Ni, SmI_2, In,[8] and $Mo(CO)_6$.[9] Several methods at reductive cleavage of isoxazolidines were attempted, including $Zn/AcOH/H_2O$ and $Pd/C/H_2$. Although the Zn reduction yielded small quantities of the amino alcohol acetate salt, the $Pd/C/H_2$ did not affect the desired transformation at all. However, when using $Mo(CO)_6$, we were able to successfully isolate the β-sultam. Initial attempts were applied to the least substituted monomer, 2-methyl-3-phenyl-isoxazolidine-4-sulfonic acid pentafluorophenyl ester, for simplicity, yielding 29% of the desired β-sultam. Although the conversion was low, we were delighted that the ring cleavage and subsequent displacement of the PFP group had occurred, in one pot and without the requirement for any additional base.

A selection of 12 isoxazolidines were subsequently screened, as shown in Table 1. Ten out of the twelve compounds successfully underwent ring cleavage and intramolecular aminolysis, resulting in the formation of β-sultams in moderate yields. Unsurprisingly, the 4-NO_2-phenyl-substituted compound did not yield any product and resulted in decomposition of starting material (Table 1, entry 11). The same was true for the pentamethyl phenyl-substituted compound (entry 12).

There are two possible mechanisms by which aminolysis may occur: (i) via a sulfene intermediate and (ii) via direct nucleophilic displacement of the PFP moiety. The former would proceed via a planar intermediate whereby the incoming nucleophile can approach from either the top or bottom face (Scheme 1). This would allow for a mixture of

Scheme 1



the cis and trans isomers of the β-sultam. If the amine approached from the underside, then protonation from the top face of the sulfene would occur, resulting in the sterically less encumbered and more stable trans isomer. However, a small amount of the cis isomer might also be expected to be isolated.

In the case of direct displacement, only the cis isomer would be expected (Scheme 2). N−O cleavage followed by rotation about the central bond allows for direct displacement of the PFP group, yielding the correct cis isomer. In this instance, the trans isomer would not occur, as we have observed. Our experimental results are consistent with a mechanism involving direct displacement of the PFP moiety.

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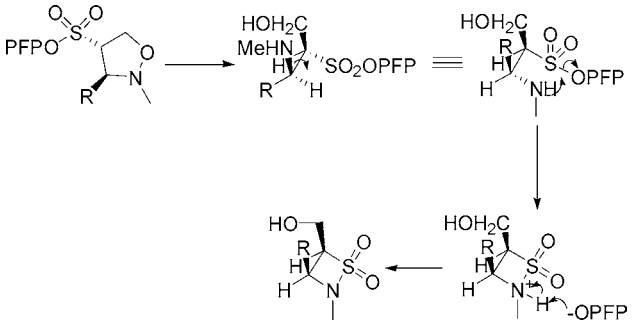
Scheme 2



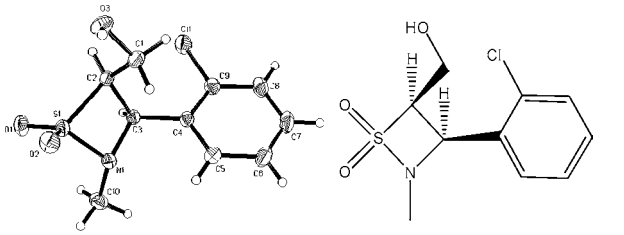


Figure 1. [3-(2-Chloro-phenyl)-2-methyl-1,1-dioxo-1λ^6-1,2-thiazetidin-4-yl]-methanol.

Confirmation of the cis stereochemistry, for **5**, was confirmed by X-ray analysis. Crystals of **5** were grown from a solution of petrol/diethyl ether via slow evaporation of the solvent, yielding colorless crystals suitable for X-ray diffraction (Figure 1).

The internal bond angle around the sulfur is 81.14(5)°, and the bond angle around the nitrogen is 93.42(7)°, consistent with that expected (79° ± 1° and 95° ± 1°, respectively).[10] The β-sultam ring is, as expected, highly strained and is bent out of linearity by 25°.

In summary, we have developed a new method for β-sultam formation, based on the selective cleavage of the N−O bond in the presence of the PFP sulfonate motif. This work not only provides a new route to β-sultams but also demonstrates the potential for carrying out selective manipulations of a PFP sulfonate ester moiety, a group which is now well-established as an alternative to sulfonyl chloride as a precursor to sulfonamides. Further work exploring chemoselective transformations of PFP sulfonates is under current investigation.

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Supporting Information Available: Experimental procedures and full analytical data for all described β-sultams. This material is available free of charge via the Internet at http://pubs.acs.org.

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