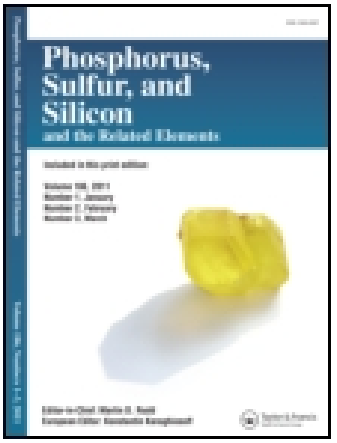

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The Quest for β-Thiolactam Antibiotics

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The Quest for β-Thiolactam Antibiotics

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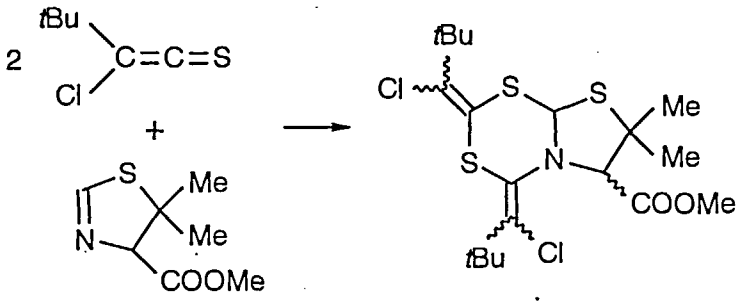
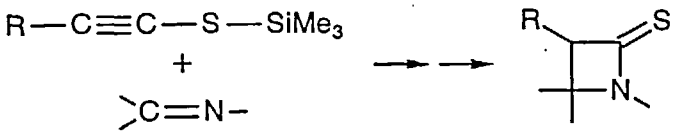
Thioketenes or thioketene equivalents give β-thiolactams in the reaction with C=N systems, but problems arise in the synthesis of highly functionalized derivatives. Therefore to obtain the thione analog of a bactam a thionation approach was chosen.

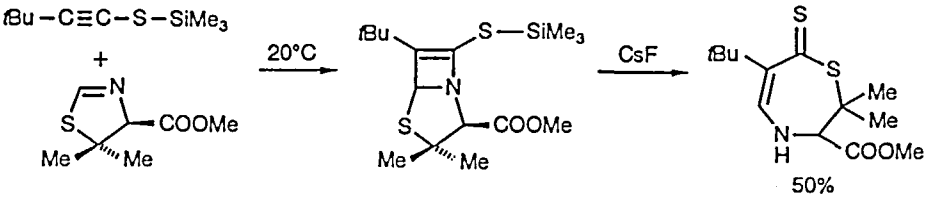
Modifications of natural β-lactams are a promising synthetic target. As to β-thiolactams, the obvious use of thioketenes in a cycloaddition approach with C=N systems is possible, but is limited to sterically hindered thioketenes. More reactive examples, e.g. tert.butyl(chloro)thioketene, tend to give 2:1 cycloadducts with azomethines or thioimidates,[1] e.g.:



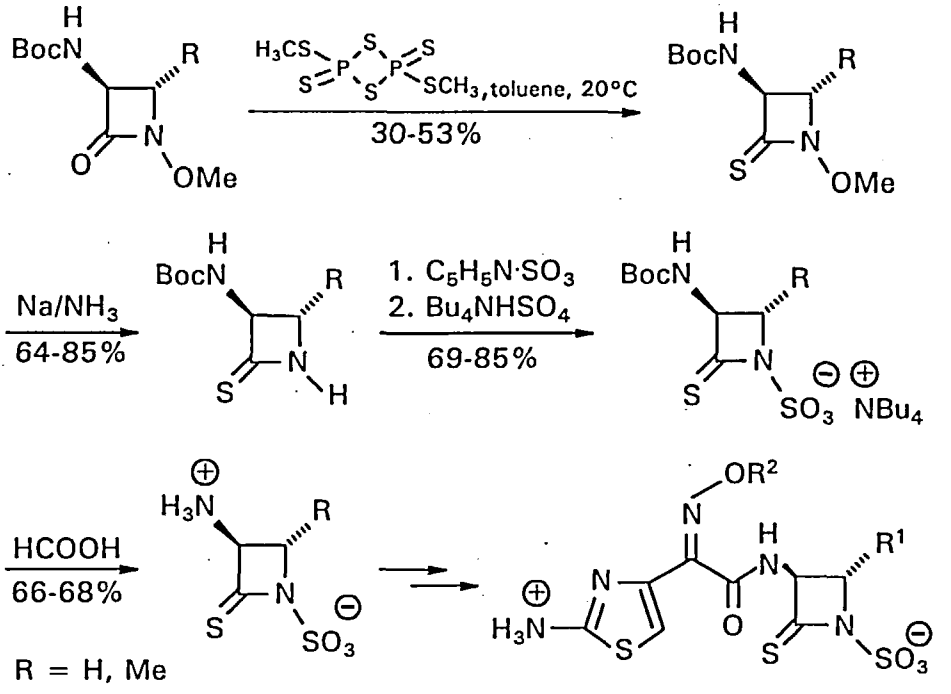
Recently, we found that alkynyl silyl sulfides are a convenient substitute for thioketenes. Interestingly, they give β-thiolactams, in the reaction with C=N systems:



Yields are variable, but can be significantly improved, if Lewis acid catalysis is employed. However, the catalysis fails if thioimidates are reaction partners. Here, a competing ring-enlargement in the desilylation step can usually not be suppressed:[2]



Therefore, to obtain a true thione analogue of a natural β-lactam, we had recourse to a thionation approach.[3] As direct thionation of β-lactam antibiotics is known to be problematic, [4] the thionation was carried out in an early stage of the synthesis. This allowed access to the thione analogues of monobactams including the antibiotic aztreonam (R = CH_3, R^2 = CMe_2COOH):



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