3-CHLORO-3-CYANO-1-(2,4-DIMETHOXYBENZYL)-4-PHENYLTHIOAZETIDIN-2-ONE

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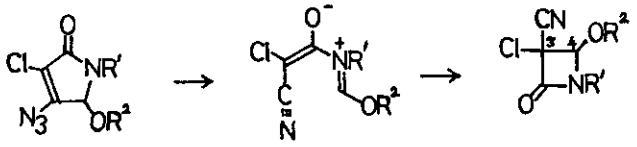
Abstract: The Moore azetidin-2-one synthetic stratagem has been further developed to give the title compound, a potentially useful synthon in β-lactam chemistry.

The Moore stratagem[1] for the synthesis of monocyclic β-lactams (Scheme) offers a potential entry into a range of precursors for analogues of the β-lactam antibiotics and β-lactamase inhibitors. We report further developmemts in the chemistry of mucochloric acid derivatives, and applications of the ring contraction method, leading to monocyclic β-lactams with a removable protecting group at N(1), and with manipulable functional groups at C(3) and C(4).



Scheme

Chloro azide (1) was reacted with 2,4-dimethoxybenzylamine to give 4-azido-3-chloro-5-hydroxy-1-(2,4-dimethoxybenzyl)-Δ^3-pyrrolinone (2) (35%). Acid catalysis did not improve the yield. Acetylation gave the acetate (3) (86%). In contrast to the Moore examples, thermolysis of (3) in dry benzene did not give a β-lactam, but afforded, instead, N-(2,4-dimethoxybenzyl)formamide (5) in 74% yield after chromatography, presumably formed by hydrolysis of (4) on the silica. Thus, intermediate (4) is too unreactive in the [2,2]-cycloaddition step. It was therefore necessary to investigate other 5-substituted variants of (2), and in particular, we targeted 5-alkyl/arylthio-Δ^3-pyrollinones (6) and (7).

Acid catalysed reaction of (2) with either ethanethiol or benzenethiol under a wide range of conditions did not give (6) or (7), but the former gave in 50% yield the 3,5-disubstituted system (8). Refluxing (8) in dry benzene gave the novel 3,3-disubstituted β-lactam (9) (84%), corroborating structure (8). Only one isomer was formed, and stereochemistry cannot rigorously be assigned on the basis of available data. Pyrollinone (8) possibly arises from Michael addition of thiol to intermediate (10).[2]

p-Nitrobenzoylation of (2) gave ester (11) (94%), which was converted to the highly reactive 5-

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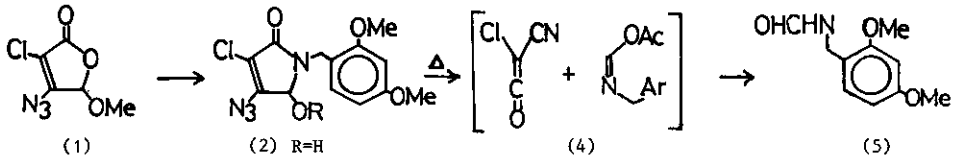
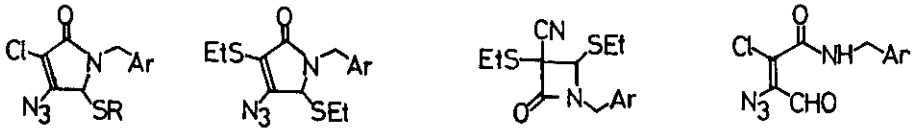
chloropyrroline (12) (dry HCl/CH_2Cl_2) which was not isolated, but reacted directly with benzenethiol to give (6) (84%). Thermolysis of (6) gave the desired β-lactam (13) (80%) as a single isomer of undefined stereochemistry.

Several other routes to (6) were examined, including reaction of mucochloric acid with thionyl chloride (best achieved in the CH_2Cl_2 in the presence of a small quantity of DMF[3]) to give mucochloryl chloride (14) and thence (15) (PhSH, $BF_3.Et_2O$, 95%), which could be progressed to the 4-azido pyrrolinone and thus a β-lactam, but this method is not as efficacious.

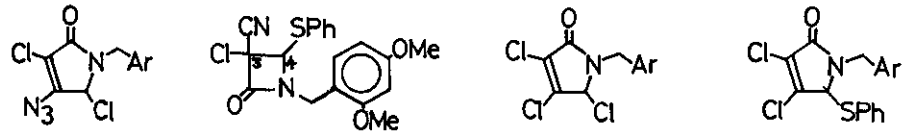
In conclusion, we have developed a route to β-lactams with substituents at N(1), C(3) and C(4) capable of being removed or modified (e.g. reductive removal of chloro,[4] or oxidative removal of N-substituent[5] and oxidation to 4-sulphone), and providing potential flexibility in the synthesis of analogues of the β-lactam antibiotics.



(1) (2) R=H (3) R=Ac (11) R=PNB (4) (5)



(6) R=Ph (7) R=Et (8) (9) (10)



(12) (13) (14) (15)

FOOTNOTE

All new compounds were characterized spectroscopically, and by elemental analysis and/or high resolution mass spectrometry analysis of homogeneous samples.

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