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SYNTHESIS OF α-HALO AND α-DEUTERIO-β-LACTAMS[1]

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A convenient synthesis of 3,3-dibromo-2-azetidinones involves the reaction of an imine with the trimethylsilyl ester of tribromoacetic acid and triphenylphosphine; reduction with n-Bu$_3$SnH and n-Bu$_3$SnD can be controlled to lead to cis-3-bromo-2-azetidinones, and cis or trans 3-deuterio-2-azetidinones.

The recent observations on the anti-β-lactamase activity of 6β-bromopenicillanic acid[2a] and α-chloropenicillanic acid sulfone[2b] have attracted the attention of synthetic chemists to α-halo-β-lactams. We have now extended our earlier studies[3] on 3-bromo-2-azetidinones and related compounds. We report here a convenient method for preparing α,α-dihalo-β-lactams and their conversion to other β-lactams of current interest.

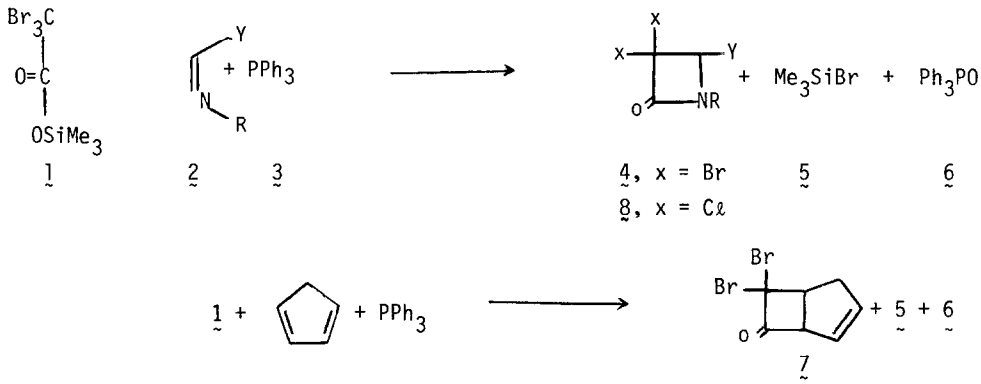
We have found that 3-3-dibromo-2-azetidinones (4) can be prepared in 50-80% yield by the reaction of a Schiff base 2 with the trimethylsilyl ester of tribromoacetic acid (1) and triphenylphosphine (3). Trimethylsilylbromide (5) and triphenylphosphine oxide (6) were identified among the other reaction products.

This reaction was designed by analogy to the synthesis of an α,α-dibromocyclobutanone compound (7) by Okada and Okawara[6] *via* the interaction of cyclopentadiene, 1 and 3.

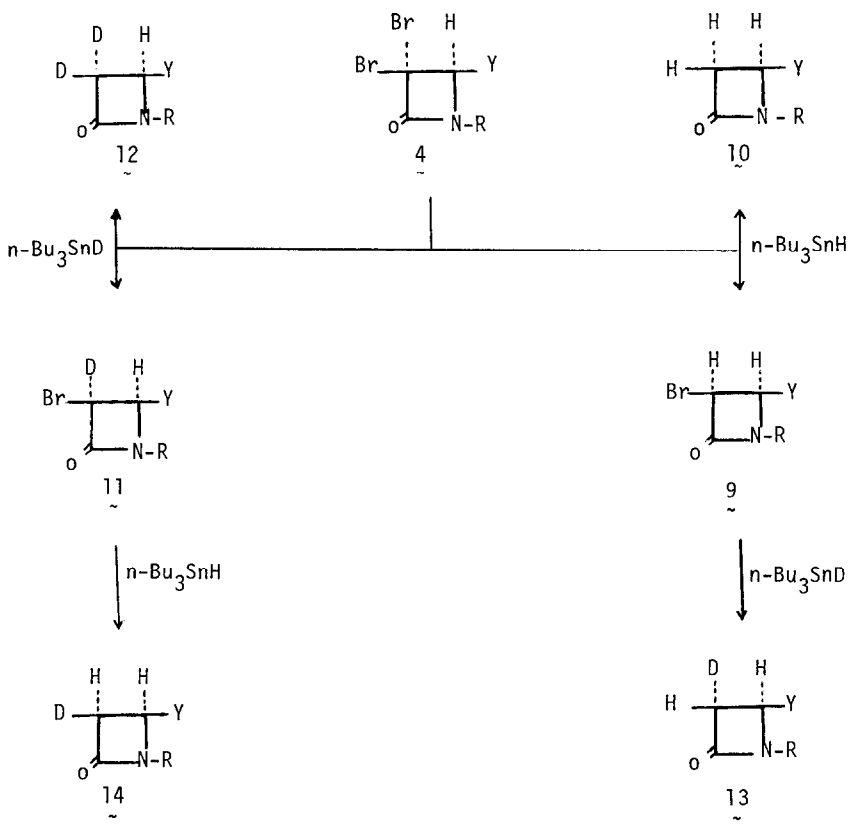
A typical experimental procedure for preparing a dibromo-β-lactam follows. The same approach can be used for the preparation of dichloro-β-lactams also.

1-(p-Tolyl)-3,3-dibromo-4-p-anisylazetidin-2-one(4,X = Br, Y = p-anisyl, R = p-tolyl):

To a stirred solution of trimethylsilyl tribromoacetate (3.69 g, 10 mmol) and N-(p-methoxybenzylidene)-p-toluidine (2.25 g, 10 mmol) in anhydrous methylene chloride (100 ml) at 0° was added dropwise a solution of triphenylphosphine (2.62 g. 10 mmol) in anhydrous methylene chloride (50 ml) under inert atmosphere. The reactants were stirred at this temperature for 1 hr. and then at room temperature overnight. After evaporating the solvent and trimethylsilyl bromide under vacuum the residue was redissolved in 100 ml methylene chloride. This solution was washed with saturated sodium bicarbonate solution and with brine and then dried ($MgSO_4$). Evaporation of the solvent followed by trituration of the crude residue with dichloromethane-alcohol mixture led to the essentially pure title compound (2.0 g, 71%) mp 159-161° (CH_2Cl_2:


Br3C
O=C
OSiMe3
+ PPh3
N
R
Y
X
NR
+ Me3SiBr + Ph3PO
4, x = Br
8, x = Cℓ
1 + + PPh3
Br
+ 5 + 6
7

Scheme 1


D H
Br H
H H
12
4
10
n-Bu3SnD
n-Bu3SnH
11
9
n-Bu3SnH
n-Bu3SnD
14
13

C_2H_5OH); Ir (Nujol): 1750 cm^{-1}; ^1H NMR ($CDC\ell_3$) δ: 2.3(s,3H), 3.85(s,3H), 5.53(s,1H), 7.1(m,8H); CMR($CDC\ell_3$), δ: 20.9($ArCH_3$), 55.3(OCH_3), 58.0(-N-C-Ar), 77.6($-CBr_2$), 114.3, 117.98, 125.2, 129.04, 129.84, 133.60, 135.23, 158.54(Aryl), 160.84(CO). Mass spec (CIMS, NH_3 reagent gas) m/z: 441, 443, 445, $(M+18)^+$ in the ratio of 1:2:1.

It was found that this β-lactam synthesis could be simplified for 3,3-dichloro β-lactams by carrying out a one pot operation. Thus, a solution of trichloroacetic acid and triethylamine in methylene chloride was treated with trimethylsilyl chloride; subsequently the Schiff base 2 (Y = R = Ph) was added along with an equimolar amount of triphenylphosphine; the desired 3,3-dichloro-1,4-diphenyl-2 azetidinone 8 (x = Cℓ, Y = R = Ph) was obtained in 63% yield. Other esters can be substituted for the silyl ester but the yield of the β-lactam was lower, for example, 8 (X = Cℓ, Y = R = Ph) was obtained in 37% yield when t-butyl trichloroacetate was utilized.

A recent publication[7] has described the preparation of 6β-bromopenicillanic acid by the stereoselective reduction of 6,6-dibromopenicillanic acid with tributyltin hydride. The monocyclic-dibromo-β-lactam 4 (X = Br, Y = p-anisyl, R = p-totyl) also showed the same type of stereoselectivity as the bicyclic β-lactam when treated with n-Bu_3SnH in benzene at room temperature: the reaction products were a single monobromo-β-lactam (9) and a halogen free β-lactam (10) (Scheme 1). The coupling constant (J = 5.5 Hz) of the protons at C_3 and C_4 in 9 showed that the β-lactam had the cis configuration.

To gain further information about the course of the reduction process, the reaction of 4 with n-Bu_3SnH was monitored at intervals by thin layer chromatography and chemical ionization mass spectrometry. No formation of a trans-bromo-β-lactam could be detected; the reduction of 4 to 9 was found to be much faster than the reduction of 4 to 10. These observations indicated the possibility of preparing 3-deuterio-2-azetidinones with complete stereocontrol. As expected, the reduction of 4 with n-Bu_3SnD led to the formation of the Z-3-bromo-3-deuterio-2-azetidinone 11 and the 3,3-dideuterio-2-azetidinone 12. The reaction of cis-3-bromo-2-azetidinone (9) with n-Bu_3SnD produced the trans-β-lactam 13; the β-lactam protons showed a coupling constant of 2.5-3.0 Hz indicating that the deuterium is trans to the C_4 - substituent. Reduction of 11 with n-Bu_3SnH, on the other hand, gave the cis isomer 14; the β-lactam protons showed the coupling constant of 5.5 Hz.

The configuration of the reduction products in the Scheme can be correctly predicted if the following assumptions are made: i) in the reaction intermediate (whether a free radical or a carbonium ion) C_3 is in the trigonal form, ii) any reagent approaching C_3 prefers the face opposite to the substituent at C_4 because of steric hindrance.

It should be noted that reactions at C-6 of various derivatives of penicillanic acid are known to result in 6α-substitution[8]. The bicyclic system of penam, resembling a half-open book, would of course offer considerable steric hindrance to the approach of any reagent to C-6 from the β-face. It is interesting that the monocyclic β-lactam 4 with only an aryl group at C-4 is equally effective in barring approach to C-3 from the same side as the aryl group.

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