NITROGEN NUCLEOPHILE DISPLACEMENTS OF THE ACETATE GROUP FROM 4-ACETOXYAZETIDIN-2-ONE

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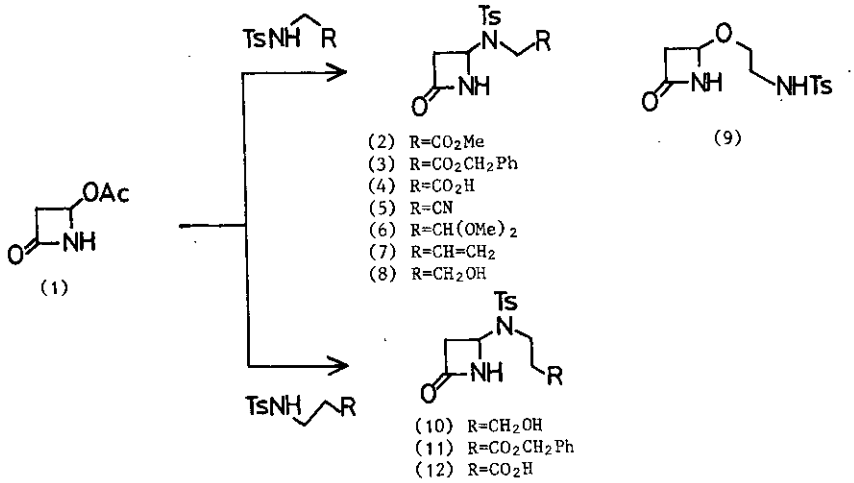
Abstract - N-Tosylamino nucleophiles displaced acetate from 4-acetoxyazetidin-2-one, complementing other studies of heteronucleophiles. Annelation procedures for model 4,6-bicyclic β-lactams were established.

Displacement by heteronucleophiles of the acetate group in 4-acetoxyazetidin-2-one (1) has led to a range of bicyclic β-lactams[1] with heteroatoms in the 1-position.† We have investigated a range of oxygen[2] and phosphorus nucleophiles[3] in such displacements, and now report a group of nitrogen nucleophile displacements which complement these studies and which afford possible precursors of 1-azapenam and 1-azacepham systems.[4]

Our previous studies showed that (L)-N-benzyloxycarbonyl alanine, as the sodium salt in a two-phase (EtOAc-H_2O) system, gave the diastereoisomers resulting from attack by carboxylate oxygen, and that with carboxy-protected aminoacids such as N-tosyl methyl glycinate with NaH as base, 4-tosylamino β-lactam (2) was formed. Subsequently, we have employed N-tosyl benzyl glycinate/ K^tBuO/18-crown-6, giving (3) (81%). Hydrogenation gave (4)†† (30%). Similarly prepared were the functionalized variants (5) - (7). It is interesting that the ambident nucleophile N-tosylethanolamine gave both possible products, (8) (30%) and (9) (12%).



(1)

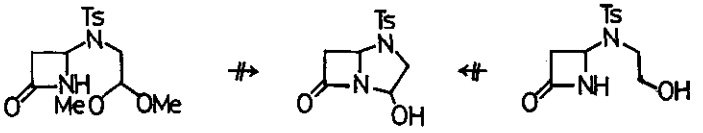
(2) R=CO_2Me
(3) R=CO_2CH_2Ph
(4) R=CO_2H
(5) R=CN
(6) R=$CH(OMe)_2$
(7) R=$CH=CH_2$
(8) R=CH_2OH

(9)

(10) R=CH_2OH
(11) R=CO_2CH_2Ph
(12) R=CO_2H

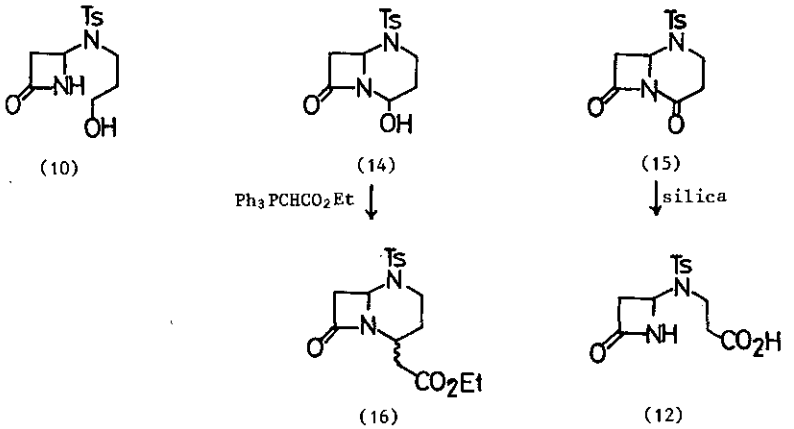
† Penicillin numbering system.
†† All new compounds were characterised spectroscopically and by elemental analysis and/or High Resolution Mass Measurement.

Oxidation of (8) to an aldehyde, and thence (13), could not be achieved under a range of mild conditions because of its instability. Similarly, (6) could not be converted into the bicyclic β-lactam (13). However, oxidation of primary alcohol (10) (pyridinium chlorochromate) gave bicyclic



(6) (13) (8)

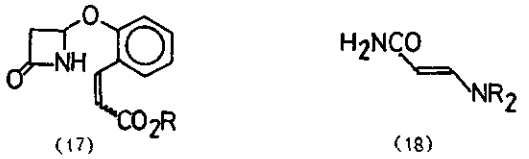
β-lactam (14) together with over-oxidized, unstable 4-oxo product (15). The former reacted, via the open chain aldehyde, with phosphoranes to give by spontaneous intramolecular Michael cyclization the inseparable diastereoisomeric bicyclic β-lactam (16). This facile annelation contrasts interestingly with the non-cyclization of (17) under a range of conditions.[2] The instability of (15) was illustrated by its facile transformation, during chromatography on silica, to (12) illustrating the greater susceptibility of the six-membered ring to cleavage under these conditions.



(10) (14) (15)

(16) (12)

These studies extend and complement other reactions[5] of secondary amines with 4-acetoxyazetidin-2-one which gave β-dialkylaminoacrylamides (18) instead.



(17) (18)

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