

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

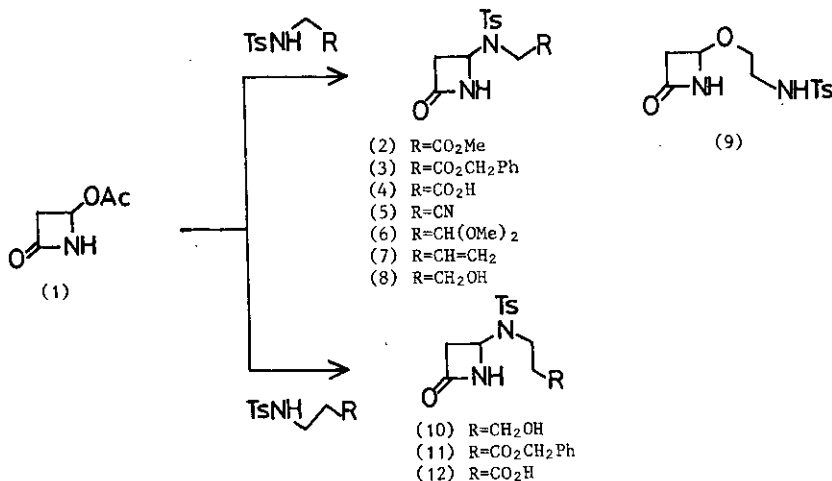
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Abstract - N-Tosylamino nucleophiles displaced acetate from 4-acetoxyazetidin-2-one, complementing other studies of heteronucleophiles. Annulation procedures for model 4,6-bicyclic β -lactams were established.

Displacement by heteronucleophiles of the acetate group in 4-acetoxyazetidin-2-one (1) has led to a range of bicyclic β -lactams¹ with heteroatoms in the 1-position.[†] We have investigated a range of oxygen² and phosphorus nucleophiles³ 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

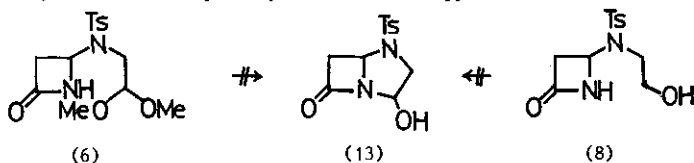
Our previous studies showed that (L)-N-benzyloxycarbonyl alanine, as the sodium salt in a two-phase (EtOAc-H₂O) system, gave the diastereoisomers resulting from attack by carboxylate oxygen, and that with carboxy-protected aminoacids such as N-tosyl methyl glycinate with NaH as base, 4-tosylamino β -lactam (2) was formed. Subsequently, we have employed N-tosyl benzyl glycinate/ K^t BuO/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%).



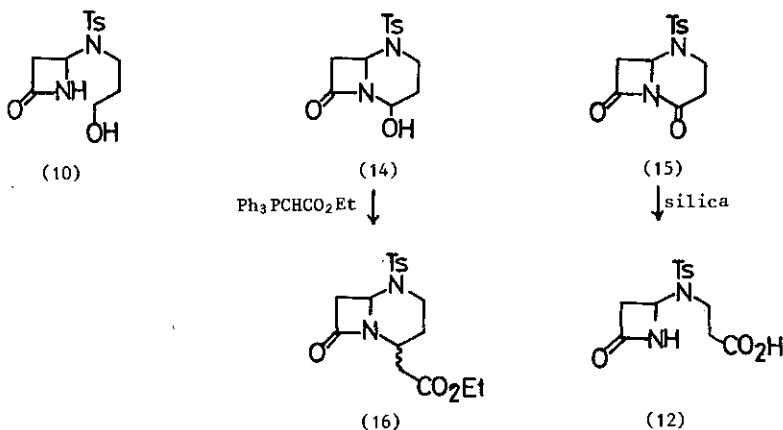
[†] Penicillin numbering system.

^{††} All new compounds were characterized 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



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.



These studies extend and complement other reactions⁵ of secondary amines with 4-acetoxyazetidion-2-one which gave β -dialkylaminoacrylamides (18) instead.



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REFERENCES

1. P.G. Sammes, 'Topics in Antibiotic Chemistry', Vol. 4, 1980.
2. M.M. Campbell and K.H. Nelson, *Chem. Comm.*, 1979, 532; M.M. Campbell and V.J. Jasys, *Heterocycles*, 1981, 16, 1487.
3. M.M. Campbell and N.T. Carruthers, *Chem. Comm.*, 1980, 730.
4. For recent syntheses in this area, see G. Johnson and B. Ross, *Chem. Comm.*, 1981, 1269.
5. M.M. Campbell, N.T. Carruthers and S.J. Mickel, *Tetrahedron*, 1982, 2165.

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