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SELECTIVE CLEAVAGE OF ESTER AND ETHER FUNCTIONS WITH BBr_3 OR Me_3SiX IN SUBSTITUTED N-ARYLAZETIDINONES

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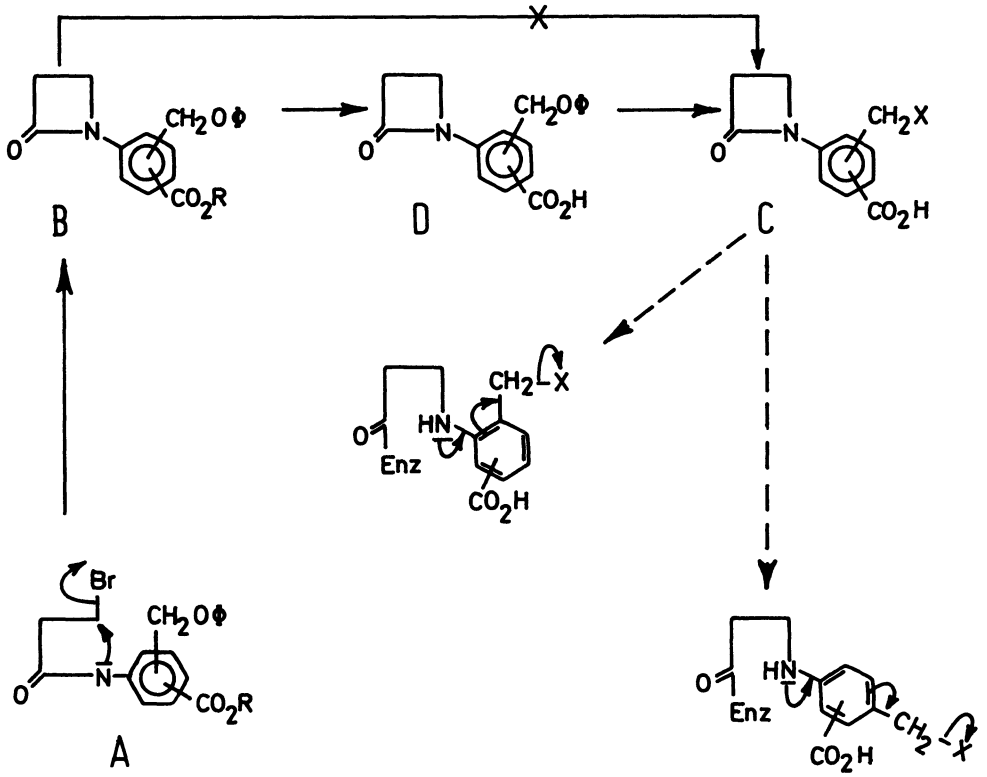
At -30°C BBr_3 is a milder reagent than Me_3SiI and Me_3SiCl + NaI for the cleavage of methyl or *tert*-butyl esters and benzyl ether group of the title β-lactams without destroying the azetidinone ring.

The resistance of bacteria to the β-lactam antibiotics is frequently due to the production of β-lactamases.[1,2] We set out to synthetize new enzyme-activated irreversible inhibitors[3,4] of these hydrolases possessing a latent reactive *ortho* or *para*-quinonimine methide group[5] which would be unmasked at the enzyme's active site as a result of the normal catalytic turnover. Compounds of type C have two structural features of a substrate for β-lactamases : an azetidinone ring and a carboxylic function. Moreover, they possess a halomethyl group, *ortho* or *para* to the nitrogen atom ; in these positions 1,4- or 1,6- elimination can occur after the ring opening step (Fig.).



o- and *p*-Halomethylanilines are unstable compounds, and cannot be used directly for the synthesis of C. We chose a phenoxymethyl group[6] as a precursor of the halomethyl substituent for two reasons : first, phenolate anion is a relatively poor leaving group and is not expected to be expelled by either 1,4- or 1,6-elimination processes during the cyclisation of the β-bromopropionanilide anion A leading to B ;[7] second, SN_2 dealkylation of a benzyl ether is a known method for the deprotection of O-benzyl tyrosine.[8]

Initially, we planned to simultaneously cleave both the ester and phenoxyl groups of B with either BX_3 or Me_3SiX reagents. Contradictory results have been recently reported with these reagents in the β-lactam field. A few examples of the cleavage of *tert*-butyl, benzyl or allyl esters with Me_3SiI[9] or BCl_3[10] have been described. The selective cleavage of a methyl ether group has been achieved with BBr_3 at low temperature.[11] However the conditions necessary to remove the benzyl or ethyl ester of substituted N-benzylazetidinones with Me_3SiCl + NaI or BBr_3 brought about the destruction of the β-lactam.[12]

We have observed that the success of these cleavages strongly depends on the structure of the β-lactam.

The reaction of N-(*p*-phenoxymethylphenyl)azetidinone 1 with Me_3SiCl + NaI in acetonitrile[13] leads to the iodide 2 (20 % yield). However in the case of arylazetidinones bearing an electronwithdrawing methoxycarbonyl substituent, the lactam carbonyl is activated and the ring is destroyed during reaction with Me_3SiI or Me_3SiCl + NaI.

Thus we turned our attention towards the BBr_3 reagent. At -30°C the ether function of 3 (B : *o*-$CH_2O\Phi$, *m*-CO_2Me) was cleaved b the methyl ester was not removed (Table), whereas at 0°C decomposition occurred.

Therefore, we carried out alkaline cleavage of the ester function before reaction with BBr_3 (B→D→C sequence). Selective mild saponification (1 eq. NaOH in pyridine[14]) of the esters 3 and 7 (B : *o*-$CH_2O\Phi$, *p*-CO_2Me) gave the acids 5 (90% yield) and 8 (45% yield). Then BBr_3 treatment in CH_2Cl_2 (4 molar eq., -30°C, 25 hrs) eventually gave 6 (48% yield) and 9 (50% yield). For the isomer 10a (B : *o*-CO_2Me, *p*-$CH_2O\Phi$) the saponification failed. Treatment of the corresponding *tert*-butyl ester 10b with 1 eq. of BBr_3 (-30°C ; 5 min) afforded 11 (C : *o*-CO_2H, *p*-$CH_2O\Phi$; 56% yield). More than one equivalent of BBr_3 led to a complex mixture of 11, 12 (C : *o*-CO_2H, *p*-CH_2Br) and ring-opened products.

Therefore in this series the reactivity order for the cleavage by BBr_3 is as follows : $CO_2tBu > CH_2O\Phi > CO_2Me$. This sequence could also allow selective deprotection of functional groups in other β-lactam synthesis.

The antibacterial activities and β-lactamase inhibitory effects of the β-lactams 2, 6, 9 and 11 and of some related compounds are currently under study.[15]

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Table

Cleavage of ester and ether groups of substituted azetidinones

n°	Starting product B or D substituent a)	Me_3SiCl + NaI	BBr_3	n°	End product C d) substituent a)	mp(°C)
1	*para*-$CH_2O\Phi$	+ b)		2	*para*-CH_2I	117-120
3	*ortho*-$CH_2O\Phi$ *meta*-CO_2Me	decomp.	+ c) -	4	*ortho*-CH_2Br *meta*-CO_2Me	d)
5	*ortho*-$CH_2O\Phi$ *meta*-CO_2H	decomp.	+ c)	6	*ortho*-CH_2Br *meta*-CO_2H	135-138
8	*ortho*-$CH_2O\Phi$ *para*-CO_2H	decomp.	+ c)	9	*ortho*-CH_2Br *para*-CO_2H	170 (decomp.)
10b	*para*-$CH_2O\Phi$ *ortho*-CO_2tBu	decomp.	- +	11	*para*-$CH_2O\Phi$ *ortho*-CO_2H	140

a) Position relative to the nitrogen.

b) To a stirred mixture of 208 mg (0.8 mmol) of 1, 120 mg (0.8 mmol) of NaI, 5 cm^3 of dry acetonitrile and 13 cm^3 of dry methylene chloride was added 86 mg (0.8 mmol) of trimethylsilyl chloride under dry nitrogen. After stirring for 15 min at 25°C, and filtration, 10 cm^3 of methanol was added and the filtrate was evaporated. 2 was purified by preparative layer chromatography (SiO_2, EtOAc).

c) To a solution of the β-lactam (0.41 mmol) in 20 cm^3 of methylene chloride at -30°C was added dropwise 0.2 cm^3 (0.2 mmol) of freshly distilled boron tribromide in 5 cm^3 of CH_2Cl_2. After stirring for 24 hrs at -30°C, the mixture was poured into 10 cm^3 of 5 % $NaHCO_3$ and the aqueous phase was acidified to pH 2 with HCl and rapidly extracted with ethyl acetate. Evaporation of the ethyl acetate produced a solid which was washed with hexane and vacuum dried.

d) Satisfactory microanalysis, IR and NMR data were obtained for all compounds except 4 which was not purified.

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