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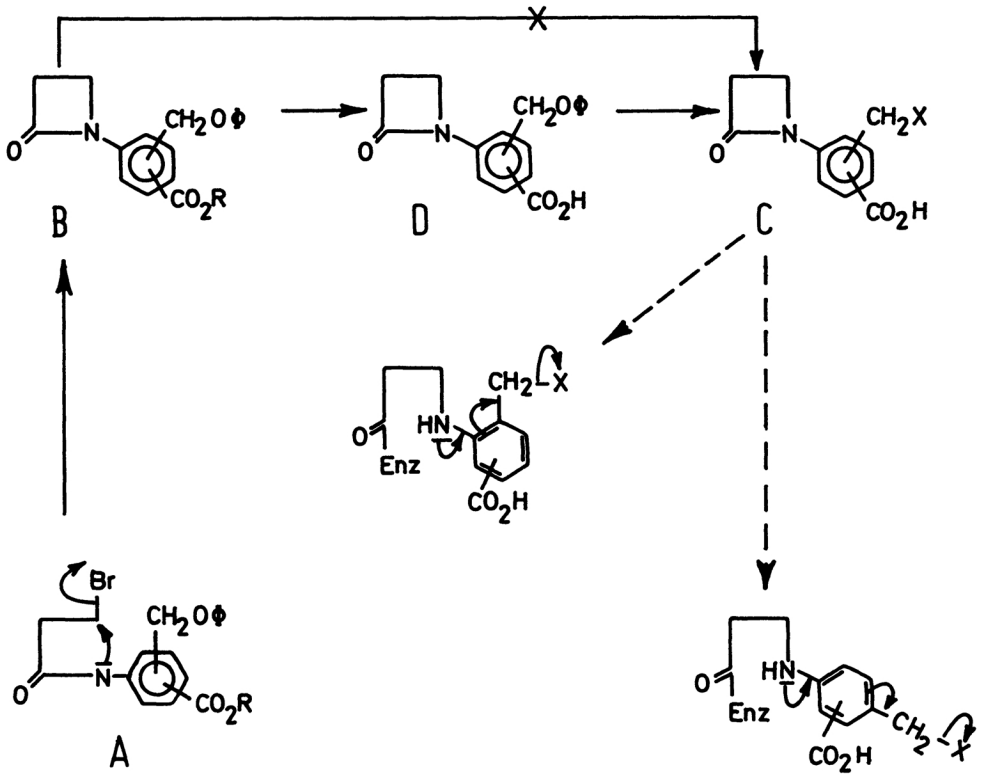
At -30°C BBr_3 is a milder reagent than Me_3SiI and Me_3SiCl + NaI for the cleavage of methyl or *tert*-butyl esters and benzyl ether group of the title β-lactams without destroying the azetidinone ring.

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.

References

1) J.M.T. Hamilton-Miller and J.T. Smith, "Beta-lactamases", Acad. Press, New York (1979).
2a) M.H. Richmond and R.B. Sykes, Adv. Microbiol. Physiol., 9, 31 (1973).
b) R.B. Sykes and M. Matthew, J. Antimicrobial. Chemother., 2, 115 (1976).
3) R.R. Rando, "Methods in Enzymology", W.B. Jacoby and M. Wilchek ed., vol. 46, p. 28 (1977).
4) N. Seiler, M.S. Jung, and J. Koch-Weser, "Enzyme activated irreversible inhibitors", Elsevier North Holland (1978).
5a) F.G. Mann and F.H.C. Stewart, J. Chem. Soc., 1954, 4127.
b) M. Wakselman and M. Dome, Bull. Soc. Chim. Fr., 1975, 571.
6) In the preparation of the starting materials, selective reduction of a nitro function in the presence of a reducible benzyl ether group has been achieved with $NaBH_4/Cu(Acac)_2$ (K. Hanaya, T. Muramatsu, H. Kudo, and Y.L. Chon, J. Chem. Soc. Perkin I, 1979, 2409). NBS bromination of N-p-tolylazetidinone does not lead to a bromomethyl derivative (NMR analysis).
7) The Wasserman procedure of cyclisation of β-bromopropionamides avoids the formation of acrylamide by-products (H.M. Wasserman, D.J. Hlasta, A.W. Tremper, and J.S. Wu, Tetrahedron Lett., 1979, 549). The preparation of the β-lactams B will be reported in the full paper.
8a) R.S. Lott, V.S. Chauhan, and G.H. Stammer, J. Chem. Soc. Chem. Comm., 1979, 495.
b) A.M. Felix, J. Org. Chem., 39, 1427 (1974).
9a) A. Nudelman, F. Braun, and E. Karoly, J. Org. Chem., 19, 3788 (1978).
b) A. Mangia and A. Scandroglio, Tetrahedron Lett., 1978, 5219.
c) R. Bonjoukian and M.L. Phillips, Tetrahedron Lett., 1981, 3915.
10) H. Yazawa, H. Nakamura, K. Tanaka, and K. Kariyone, Tetrahedron Lett., 1974, 3991.
11) S.J. Daum and P.E. Hansen, Synthetic Comm., 11, 1 (1981).
12) P.G. Mattingly and M.J. Miller, J. Org. Chem., 46, 1557 (1981).
13a) T. Morita, Y. Okamoto, and H. Sakurai, J. Chem. Soc. Chem. Comm., 1978, 874.
b) G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, J. Org. Chem., 44, 1247 (1979).
14) R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews, J. Am. Chem. Soc., 91, 1401 (1969).
15) M. Zrihen, M. Wakselman, and R. Labia, in preparation.

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