6-β-[BISTRIFLUOROMETHANESULFONYL]AMIDOPENICILLANIC ACID. A NOVEL β-LACTAMASE INHIBITOR

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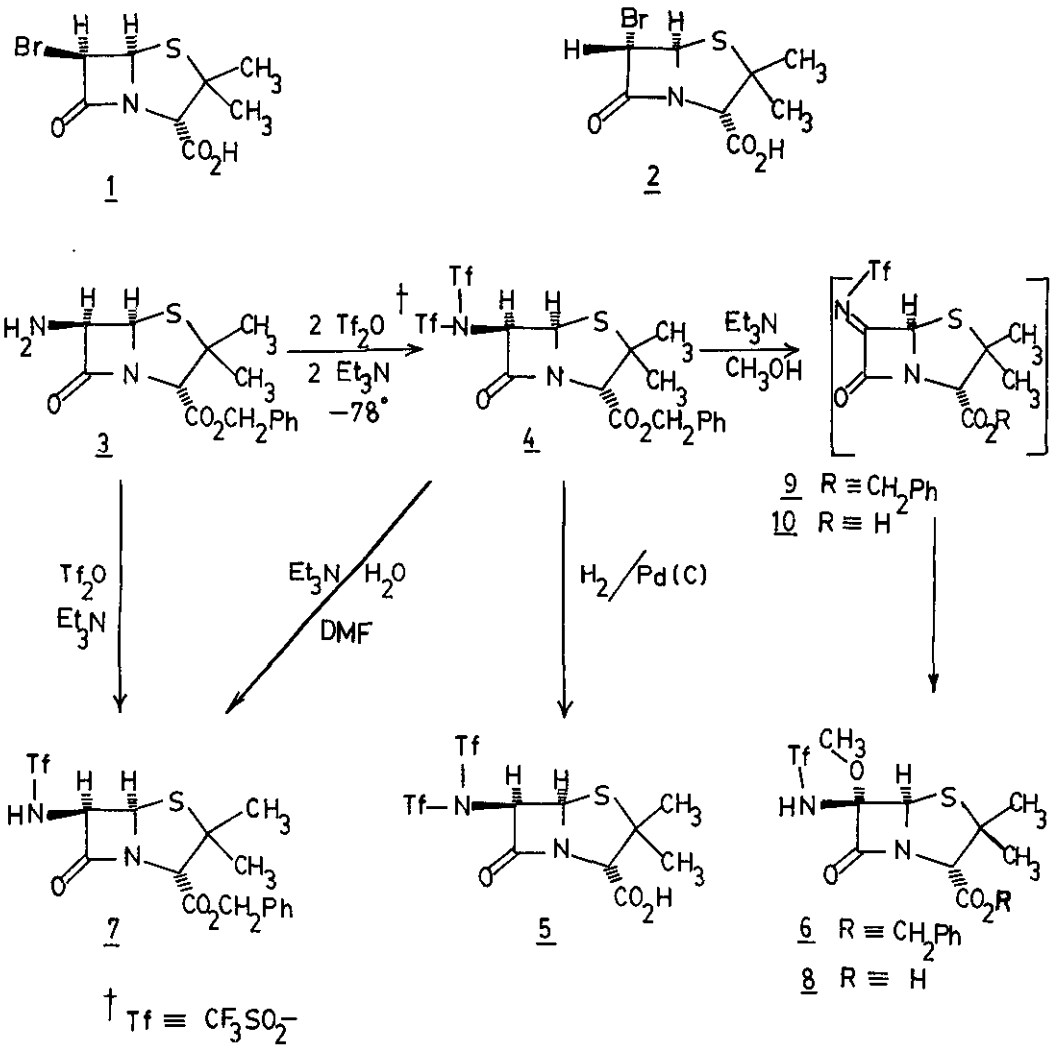
Abstract - Benzyl 6-β-[bistrifluoromethanesulfonyl]amidopenicillanate, 4, was prepared by reaction of benzyl 6-β-aminopenicillanate, 3, with two equivalents of trifluoromethane sulfonic anhydride. In the presence of aqueous base 4 undergoes detriflation to yield 7 and in the presence of basic methanol 4 yields the α-methoxymonotriflamide 6. The free acid 5 obtained by hydrogenolysis of 4 has β-lactamase inhibitory properties.

The limitations imposed on the chemotherapeutic applications of penicillins by the ability of bacteria to produce enzymes, β-lactamases, which inactivate β-lactam antibiotics, were recognized some time ago.[1] In recent years there has been significant progress made towards overcoming this problem through the development of effective β-lactamase inhibitors derived directly from natural sources[2] and also derived from natural penicillins through chemical modification.[3]

Pratt and Loosemore[4] and also Waley and coworkers[5] have reported that 6-β-bromopenicillanic acid 1 is a potent inhibitor of β-lactamases. The early reports indicated that 1 could be synthesized only as a minor component (< 28%) of a mixture containing the $C_{6\alpha}$ epimer, 2, and that the epimers could not be separated.[6] Because of our continuing interest in the inhibition of β-lactamases[7], we undertook a study aimed at the design and synthesis of analogs of 1 which would possess a potential leaving group at C_6 and which could be prepared as pure $C_{6\beta}$-isomers. We report herein the preparation and reactions of one such analog 5. The known tendency of bistriflamido groups to function as leaving groups in S_N2 type displacement reactions[8] suggested that 5 might behave chemically (and hopefully biochemically) as an analog of 1.

Treatment of the benzyl ester of 6-β-aminopenicillanic acid 3 with two equivalents of freshly distilled triflic anhydride at -78° in methylene chloride containing two equivalents of triethylamine yielded after aqueous workup the bistriflamide 4 as a crystalline solid (i.r. 1810 (β-lactam), 1750 (ester); ^{1}H n.m.r. δ(CDCl$_3$) 1.45 (s, 3; $C_{2\alpha}$ or $_{\beta}$-CH_3), 1.72 (s, 3; $C_{2\beta}$ or $_{\alpha}$-CH_3) 4.52 (s, 1; C_3-H), 5.20 (s, 2; OCH_2-Ph), 5.48 (d, J = 4.1; C_5-H), 5.73 (d, J = 4.1; C_6-H) 7.37 (s, 5; ArH). Anal. Calcd. for $C_{17}H_{17}N_2O_7S_3F_6$: C, 35.78; H. 2.83; N, 4.91; S, 16.86; F, 19.98;



Found: C, 36.06; H, 2.96; N, 4.88; S, 16.98; F, 19.67.) ^{19}F n.m.r. 7.80 relative to external CF_3CO_2H (s, CF_3SO_2N).

It was clear from the proton and ^{13}C n.m.r. that 4 was obtained as a single epimer with the β-configuration ($J_{5,6}$ = 4 Hz) at C-6. C-6-α-epimers show a smaller ($J_{5,6}$ = 1-2 Hz) coupling[4]. Hydrogenolysis of 4 in methanol yielded the free acid 5. Preliminary experiments have indicated that 5 is capable of rapid complete inhibition of β-lactamase-I from B. cereus 569/H at inhibitor concentrations on the order of 10^{-5} molar[9].

Since we expected that the β-lactamase inhibitory action of 5 involved reaction with an enzyme-bound nucleophilic group we examined the base catalyzed reaction of 4 with water and methanol. Two reaction modes have come to light. With triethylamine in aqueous DMF, 4 acts as a triflating agent towards water yielding the monotriflamide 7 which was also obtained by monotriflation of 3. The free acid 8 had no β-lactamase inhibitory properties but interestingly is apparently β-lactamase resistant.

In methanol containing excess triethylamine, 7 was obtained as a minor product (~5%). The major product was the 6-α-methoxymonotriflamide 6 (^{1}H n.m.r. 1.40 (s, 3, $C_{2\alpha}$ or $_{\beta}$-CH_3), 1.58 (s, 3, $C_{2\beta}$ or $_{\alpha}$-CH_3), 3.60 (s, 3, OCH_3), 4.54 (s, 1, C_3-H), 5.21 (s, 2, Ar-CH_2O-C-), 5.53 (s, 1, C_5-H), 7.38 (s, 5, Ar-H) ^{19}F n.m.r. 0.42 (s, $(CF_3SO_2)_2N$)) which presumably arises via an elimination-addition sequence via 9 as shown. The stereochemistry of 6 is assumed to be α at C-6 by analogy with the known stereoselectivity of additions of alcohols to 6-acyliminopenicillanic acid derivatives.[10] Analogous elimination-addition reactions have been observed with N,N-bisaryl-sulfenylaminopenicillanic acid derivatives which also show some β-lactamase inhibitory activity.[1]

These observations suggest the possibility that triflation of a key functional group of the β-lactamase by 5 or alkylation by 10 derived from 5 may account for the β-lactamase-inhibitory properties of the bistrifamide 5. Detailed chemical and spectroscopic studies of the inhibition process are in progress. In addition the possible utility of the elimination process, 4 → 9 in the preparation of 6α-alkoxypenicillins or 7α-alkoxycephalosporins is under investigation.

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