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DIRECT INCORPORATION OF A 6α(7α)-FORMAMIDO GROUP INTO PENICILLINS AND CEPHALOSPORINS

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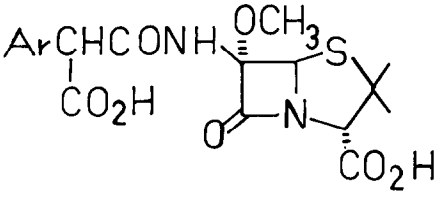
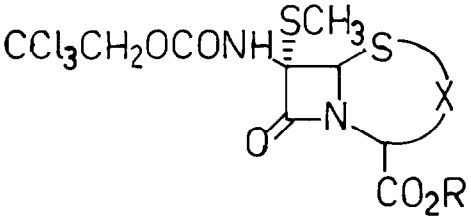
Summary: 6β(7β)-(N-2,2,2-Trichloroethoxycarbonyl-N-trifluoromethanesulphonylamino) penicillins and cephalosporins have been converted into the corresponding 6α(7α)-formamido-6β(7β)-2,2,2-trichloroethoxycarbonylamino derivatives, by treatment with N,N-bis(trimethylsilyl) formamide and triethylamine.

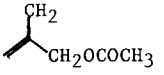
It is well known that the introduction of a methoxy substituent into the 7α-position of a cephalosporin provides compounds with enhanced activity against certain Gram-negative organisms.[1] With the exception of aryl malonic acid derivatives (1),[2] insertion of the same functionality into the 6α-position of penicillins is of little utility. Replacement of methoxy by a diverse range of functional groups generally leads to compounds of less biological interest.[1] However, recent work in these laboratories indicates that a 6α(7α)-formamido group is superior to methoxy in imparting potent bioactivity to certain penicillins and cephalosporins.[3,4] We now wish to report the conversion of benzyl 6β-aminopenicillanate into the crystalline 6α-formamido derivative (4) via a three step process, which does not necessitate chromatography, in an overall yield of more than 50%. The methodology can also be applied to the cephalosporin series, but a problem of double bond isomerisation was encountered at the final stage.



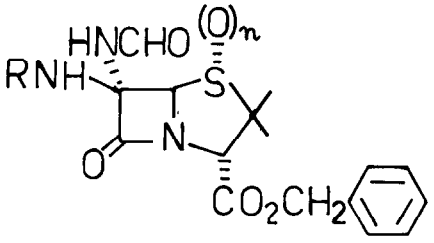
(1)



(2) X = $C(CH_3)_2$, R = CH_2Ph

(3) X =  , R = $C(CH_3)_3$

In our initial studies[4], the 6α(7α)-methylthio derivatives (2) and (3) were found to be convenient precursors for the introduction of the 6α(7α)-formamido functionality, via a mercury (II) mediated displacement in the presence of N,N-bis(trimethylsilyl)formamide (BSF). However, a more direct route, avoiding prior 6α(7α)-functionalisation of the β-lactam, was required. Although several methods are available for a single step incorporation of a 6α(7α)-methoxy substituent into 6β(7β)-acylamino penicillins and cephalosporins,[1] none were particularly efficient for the insertion of a formamido group.

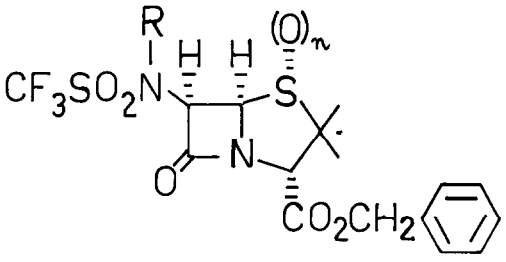


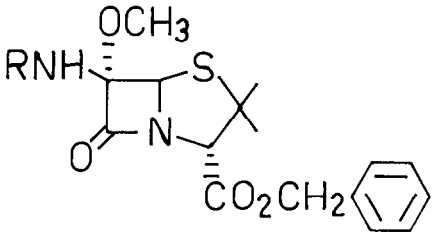
(4) R = $CO_2CH_2CCl_3$, n = 0

(5) R = H, n = 0

(6) R = $CO_2CH_2CCl_3$, n = 1

Recently it has been shown that treatment of the bis-triflamide (7) with excess triethylamine in methanol gives the 6α-methoxymonotriflamide (11) as the major product.[5] Since the 2,2,2-trichloroethoxycarbonyl group affords convenient protection for the 6β(7β)-amino functionality of 6α(7α)-formamido penicillins and cephalosporins, the intended strategy involved the synthesis of a derivative of type (9). It was then surmised that treatment of (9) with BSF and triethylamine might afford the 6α-formamido penicillin (4). Removal of the amino protecting group would then allow derivatisation of the nucleus (5).





(7) R = SO_2CF_3, n = 0

(8) R = H , n = 0

(9) R = $CO_2CH_2CCl_3$, n = 0

(10) R = $CO_2CH_2CCl_3$, n = 1

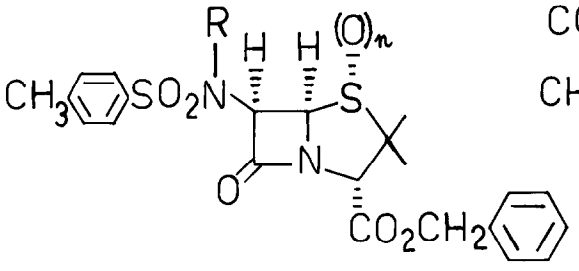
(11) R = SO_2CF_3

(12) R = $CO_2CH_2CCl_3$

Accordingly, the monotriflamide (8)[5] was treated in methylene dichloride (MDC) with (2,2,2-trichloroethoxy)carbonyl chloride and triethylamine, in the presence of a catalytic quantity of 4-(N,N-dimethylamino)pyridine [2h, 20°C]. The 6β-bisfunctionalised derivative (9) was isolated as a crystalline solid in 91% yield, mp 89-90°C; ν_{max} ($CHCl_3$) 1880, 1780, and 1750cm^{-1}; δ_H($CDCl_3$) 1.43 (3H, s), 1.69 (3H, s), 4.57 (1H, s), 4.86 and 4.95 (2H, ABq, J 11.5Hz), 5.20 (2H, AA'), 5.50 (1H, d, J 3.9Hz), 5.5 (1H, d, J 3.9Hz), and 7.38 (5H, s). Reaction of (9) with BSF (2 equiv) and triethylamine (1.5 equiv) in MDC [2h, 0 → 20°C] provided the crystalline carbamate (4) (84%), identical to that obtained *via* the 6α-methylthio derivative (2).

Incorporation of a 6α-methoxy group was also demonstrated. Thus, reaction of (9) with triethylamine (1.2 equiv) in MDC -methanol (3:1) afforded (12) (69%), ν_{max} ($CHCl_3$) 3420, 1778, and 1745cm^{-1}; δ_H($CDCl_3$) 1.36 (3H, s), 1.48 (3H, s), 3.5 (3H, s), 4.45 (1H, s), 4.73 (2H, AA'), 5.15 (2H, s), 5.52 (1H, s), 6.26b (1H, s, exch. D_2O), and 7.30 (5H, s). Use of excess triethylamine (3.3 equiv) in neat methanol was detrimental.

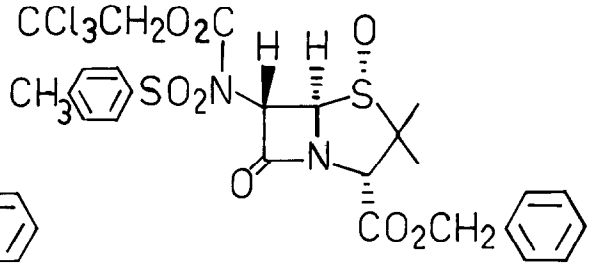
The utility of a group less electron withdrawing than trifluoromethanesulphonyl was also examined. The p-toluenesulphonamide (13)[6] was further functionalised by treatment with 2,2,2-(trichloroethoxy)carbonyl chloride and pyridine in MDC, but the product (14) slowly decomposed on reaction with BSF-triethylamine, without formamido incorporation. However, similar treatment [20°C, 20min] of the α-sulphoxide (15), prepared by peracetic acid oxidation of (14), afforded the 6α-formamido sulphoxide (6) (45%), and some C(6)-epimerised material (16) (40%). The activation of the C(6)-proton by oxidation of the thiazolidine sulphur is well documented.[7]



(13) R = H, n = 0

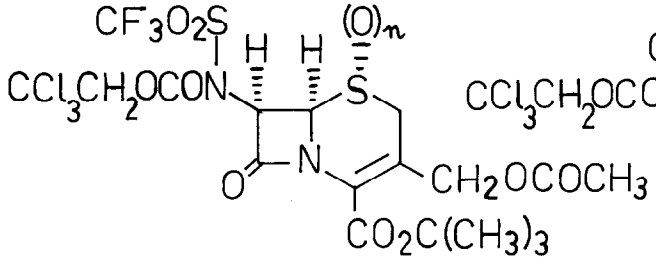
(14) R = $CO_2CH_2CCl_3$, n = 0

(15) R = $CO_2CH_2CCl_3$, n = 1



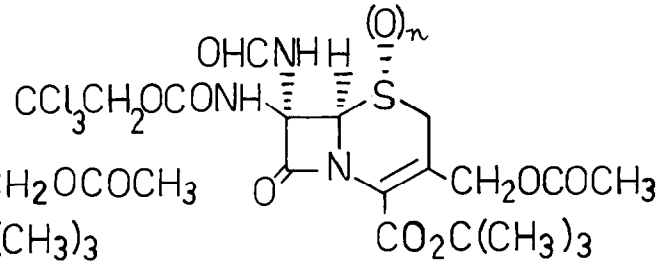
(16)

In general the incorporation of a 7α-formamido group was more facile in the cephalosporin series. The 7β-bisfunctionalised compound (17) was prepared as described for (9), and treated with BSF (2 equiv) and triethylamine (1.1 equiv) in MDC (-10°→ 0°C,2h) to afford the 7α-formamido cephalosporanate (19) (55%), containing ca. 10% of the Δ-2 isomer (21).



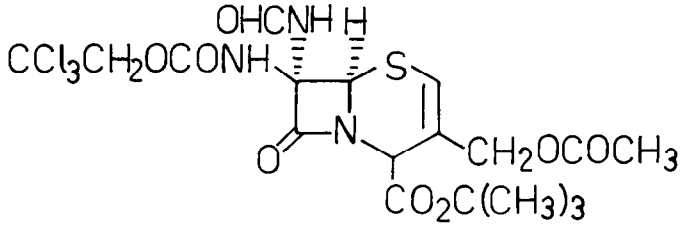
(17) n = 0

(18) n = 1



(19) n = 0

(20) n = 1



(21)

Predictably, incorporation of a 7α-formamido group into the α-sulphoxide (18) gave only the Δ-3 sulphoxide (20), albeit in low yield (25%). Reduction of (20) with phosphorous trichloride[8] in MDC [0°C, 45min] provided the pure sulphide (19). The trifluoromethyl group of (17) could be replaced by nonafluorobutyl, pentafluorophenyl, 2,4-dinitrophenyl, and 4-nitrophenyl, in decreasing order of effectiveness. These results will be reported in a full paper.

References and notes.

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