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A CONVENIENT LARGE SCALE SYNTHESIS OF 7α-FORMAMIDO CEPHALOSPORINS

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Abstract: The development of a convenient "one pot" synthesis of 7α-formamido ACA(12) from 7-ACA(2) via quinone methide methodology is described.

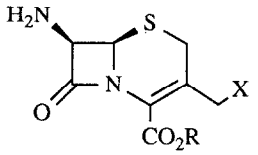
In earlier publications[1,2] we have reported the preparation and antibacterial activity[3,4] of some 7α(6α)-formamido cephalosporins and penicillins. We have been interested in improving the syntheses of these potent, β-lactamase stable antibiotics as most routes currently used require tedious pre-functionalisation[5] of the 7α(6α)position prior to introduction of the formamido group. A recent publication by Kamachi *et al*[6] on the direct introduction of the formamido group into protected cephalosporins/penicillins has now prompted us to report our own studies[7] in the area. Like Kamachi *et al*[6] we have utilised the quinoid methodology originally developed by Yanagisawa *et al*[8] for the preparation of 7α-methoxy cephalosporins, and for convenience we concentrated initially on t-butyl protected cephalosporanates.

Oxidation of the Schiff base(5) (prepared by condensation of t-butyl cephalosporanate(1) with 3,5-di-t-butyl-4-hydroxy benzaldehyde(4)) with freshly prepared lead dioxide (toluene;R.T) afforded the quinone methide(9), which is conveniently used *in situ* after filtration, but may be isolated in a pure form[9] by chromatography on silica gel. Reaction with the nucleophilic formamide equivalent, *N,N*-bis(trimethylsilyl)-formamide[1,10] (BSF) (4h;R.T) gave the 7α-formamido derivative(6) in 58% yield. Hydrolysis of the benzylidene group with toluene-4-sulphonic acid and Girard reagent T afforded the t-butyl 7α-formamido cephalosporanate(11), identical in every respect to authentic material[2] and with no sign of the Δ^2 isomer.

We next sought to improve the process for use on a large scale, and firstly investigated alternative oxidising agents. Silver oxide failed to produce any of the desired product. Oxidation of Schiff base(5) with freshly prepared MnO_2[11] (20 equivalents), followed by prolonged (16h) reaction with BSF, did afford the 7α-formamido derivative(6) (13% yield) in addition to the 7-epi compound(14) (9% yield) (confirmed by hydrolysis to the 7β-formamido isomer(15)[9]). We subsequently found 7-epi formation to be a consequence of prolonged reaction with BSF, as this also occurred when PbO_2 was used under these conditions. An improvement in the reaction was found when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used to effect the oxidation. Not only was DDQ more convenient to handle than heavy metal oxidants, it also gave a

purer product in better yield. By use of DDQ, the versatile 3-chloromethyl cephalosporanate(3)[12] has been converted to its 7α-formamido counterpart(13) (isolated as the toluene-4-sulphonic acid salt) in an overall yield of 67% from (3), without the need for isolation and purification of intermediates.

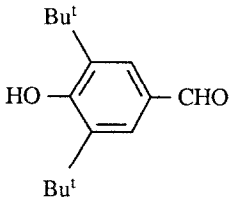
However our main objective was a direct synthesis of the 7α-formamido nucleus(12) from 7-ACA(2) itself, since such free acids are generally more amenable to C(3) modification than the corresponding esters[13]. We found that this could be achieved by the use of labile trimethylsilyl(TMS) ester protection. Reaction of 7-ACA(2) with *N,O*-bis(trimethylsilyl)acetamide(BSA) (1.6 equivalents; CH_2Cl_2; 30 mins; R.T), followed by treatment with the aldehyde(4) in the presence of HBr/HOAc catalyst, led to quantitative formation of the Schiff base TMS ester(7) within two minutes of addition of the catalyst. Subsequent oxidation *in situ* with DDQ (1 equivalent; 0.5-1h; R.T) gave the quinone methide(10) which, after filtration of the precipitated hydroquinone, could be treated with BSF (3 equivalents; 2h; R.T) to yield the 7α-formamido Schiff base(8) with no Δ^2 isomerisation. Addition of just sufficient water(1.2 equivalents) for hydrolysis of the silyl groups caused precipitation of 7α-formamido ACA(12). Crystallisation from pyridine/water/acetone after adjustment to pH 2.5, afforded the pure nucleus(12) identical in all respects to authentic material[2]. This "one-pot" preparation of 7α-formamido ACA(12) from 7-ACA(2) has given yields of 46% on a 1kg. scale. This process also has the advantage that the DDQ and the aldehyde(4) are recoverable and recyclable.



(1) R = Bu^t , X = OAc

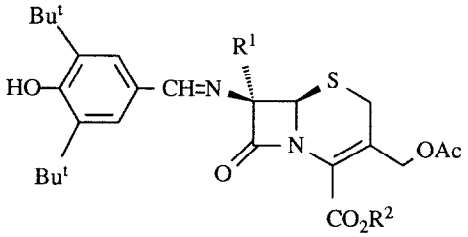
(2) R = H , X = OAc

(3) R = PMB , X = Cl



(4)

[PMB = 4-Methoxybenzyl]

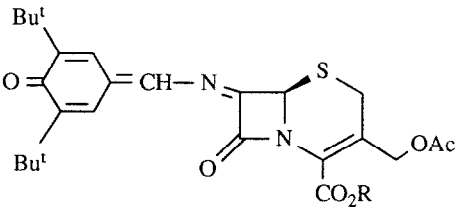


(5) R^1 = H , R^2 = Bu^t

(6) R^1 = NHCHO, R^2 = Bu^t

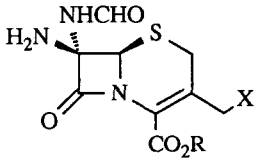
(7) R^1 = H , R^2 = $SiMe_3$

(8) R^1 = NHCHO, R^2 = $SiMe_3$



(9) R = Bu^t

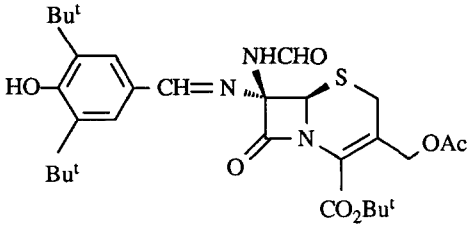
(10) R = $SiMe_3$



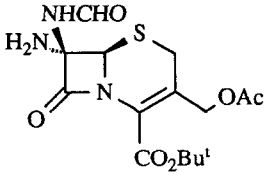
(11) R = Bu^t , X = OAc

(12) R = H , X = OAc

(13) R = PMB , X = Cl



(14)



(15)

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9. All isolated compounds exhibited satisfactory microanalytical and/or spectroscopic properties. Selected physical data are as follows:
(9):$\nu_{(max)}$.(CH_2Cl_2) 1770, 1735, 1725, 1680, 1610 cm^{-1}; δ($CDCl_3$) 1.30 (9H, s), 1.33(9H, s), 1.60(9H, s), 2.12(3H, s), 3.45 and 3.65(2H, ABq, J 18.5 Hz.), 4.84 and 5.10(2H, ABq, J 13 Hz.), 5.39(1H, br.s), 6.98(1H, d), 7.90(1H, br.s), 8.04(2H, br.s).
(15):δ($CDCl_3$) 1.56(9H, s), 2.09(3H, s), 2.20(2H, br.s), 3.34 and 3.55(2H, ABq, J 17.8 Hz.), 4.82 and 4.99(2H, ABq, J 13.1 Hz.), 5.11(1H, s), 6.76(1H, br.s), 8.26(1H, d, J 0.8 Hz.)

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