DISPLACEMENT WITH NITROGEN NUCLEOPHILES AT C-3' of 7-AMINOCEPHALOSPORANIC ACID AND DERIVATIVES PROMOTED BY TRIALKYLSILYL TRIFLUOROMETHANESULPHONATES°

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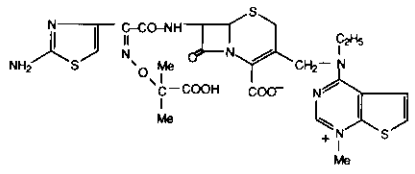
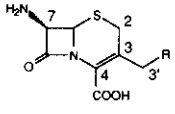
Abstract- Replacement of a 3'-acetate group of a cephem by an alkylamino group can be mediated by trialkylsilyl trifluoromethanesulphonates in dichloromethane or acetonitrile inter alia. Comparable yields to the more usual 3'-iodo routes have been achieved, using a quick and simple procedure.

ICI 194008(1)[1] is a broad spectrum, injectable, aminothiazolyl cephalosporin. A possible route to this compound involves the transformation of 7-aminocephalosporanic acid (7-ACA) (2a) to 3-ethylaminomethyl-7-aminocephalosporanic acid (EAMACA) (2b).

Considerable interest has been shown in the replacement of the 3'-acetoxy group of cephalosporins by oxygen and sulphur nucleophiles, and in the introduction of nitrogen where a charged 3'-species results e.g. cephaloridine[2]. Conversions such as 2a to 2b have not received attention. One approach would involve the intermediacy of the more reactive 3-iodomethylcephems (e.g. 2c) either as a distinct preparative step or by in situ generation (the one-pot process)[3]. As part of a general study of the conversion of 2a to 2b a number of approaches was investigated in our laboratories[4]. These included the use of trimethylsilyl iodide (TMSI) and the related strategy of using trialkylsilyl trifluoromethanesulphonates (triflates). It was reasoned that potent silylating agents such as triflates should promote the leaving group ability of the 3'-ester by way of an incipient carbonium ion (Scheme I). Related findings have been published[5] recently by other workers. For the initial studies,



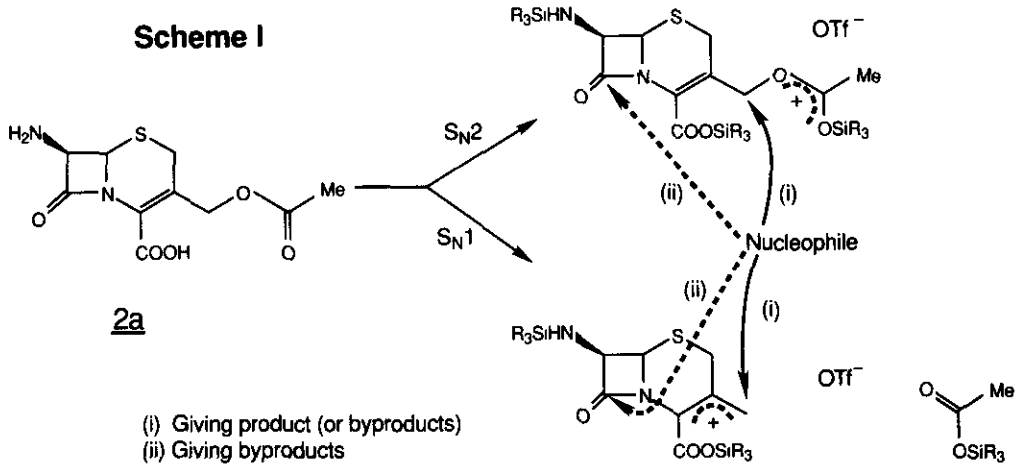
1 ICI 194,008



2 a R=OAc c R=I
b R=NHEt d R=OH

° Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

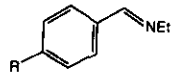
Scheme I



N-ethylbenzaldimine (3a)[4,6] was chosen rather than ethylamine as both base and nucleophile in order to reduce competing reactions, such as β-lactam ring opening and ^{2}-isomerisation.

With trimethylsilyl triflate (TMSOTf) results were immediately encouraging. After initial optimisation of stoichiometry, temperature and solvent (Table I), the following basic method was adopted:-

N-Ethylbenzaldimine (4.5 equivalents) was added to a stirred suspension of 7-ACA (5g) in CH_2Cl_2 (100 ml) at room temperature, followed by TMSOTf (4.5 eq.) added over 15 minutes. A slight exotherm caused the temperature to rise to 26-28°C. After 2 hours, the conversion appeared clean and complete by hplc. The reaction mixture was drowned into water (300 ml) containing sodium acetate (3 eq.), stirred vigorously for 15 min., washed with CH_2Cl_2 (2 x 150 ml), adjusted to pH 5.0 with glacial acetic acid and pre-adsorbed onto Sepabeads $^{R\ 7}$ (2 x 200 ml), discarding the supernatant liquor. Elution off these Sepabeads through a further 1000 ml of Sepabeads, first with H_2O, then with 2% MeCN/H_2O at 15 ml/min., gave 2b in 38% yield after freeze-drying. Despite the modest yield, the operational simplicity and the absence of both lactone (4) and 7-desacetylcephalosporanic acid (2d) by-products (hplc) pointed to potential advantages.



3 : a · R = H c. R = OMe
b · R = NO_2 d · R = ^{t}Bu

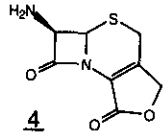


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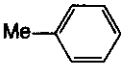
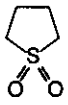
Table I Optimisation of reaction conditions for 2a→2b with regard to stoichiometry and temperature

PhCH=NEt 3a (eq)	12[a]	6	6	6	3	4 5 (or 6)	6	6	4.5	4
TMSOTf (eq)	5	3	4	5	5	5	5	5	4 5	3 5
Reaction temp (°C)	0	0	0	0	10 ↓ 23	10 ↓ 23	5 then 23	23	Reflux	−20 then 23
Reaction time (h)	5.5	5	5	4	0.5 then 5	0 5 then 5	6 then 0.5	1	0 5	2
Relative yield (hplc peak area ratio)	1.0	0.1	0.9	0.9	0.8	0 9	1.1	1 2	0 5	0 13

a) Added in two portions[6]: 3a (6 eq.), then TMSOTf (5 eq.), then 3a (6 eq.)

Table II Effect of varying solvent for 2a → 2b using N-ethylbenzaldimine (3a) (4.5 eq.) and TMSOTf (4.5 eq.) at 23°C.

Solvent	CH_2Cl_2	MeCN	$MeNO_2$	Me- 		DMF or DMPU	SO_2[b]
Reaction time (h)	<2	<0.5	>5	>5	>5	>5	>5
Relative yield (hplc peak area ratio)	1.0	>1.0	0.7[a]	low	low	low[a]	low[a]

a) 7-ACA remained unreacted after several hours.

b) Carried out at -10°C (liquid SO_2).

Clearly from Table II, the reaction proceeded faster in acetonitrile than in dichloromethane with no loss of yield. None of the other solvents or the various addition modes tried (simultaneous or inverse addition, pre-mixing of imine and triflate or *in situ* generation[8] of triflate from tetramethylsilane and triflic acid) in CH_2Cl_2 gave comparable results.

Other factors which might influence the yield were considered. Tempering the reactivity of the 7-amino group (pK_a 4.4) of 7-ACA by Schiff base formation[9], gave decreased yields of

product (hplc estimation). However, the use of bulkier silyl groups, to afford more stable N-protection and reduce the likelihood of β-lactam ring opening, proved more successful. Results are summarised in Table III. Whereas t-butyldimethylsilyl triflate was equivalent in efficacy to TMSOTf, tri-isopropylsilyl triflate (TIPSOTf)[10] gave greatly increased hplc yields, and, with optimised work-up conditions (vide infra), isolated yields. Again acetonitrile as alternative solvent gave a very rapid reaction (5 min.), but the relative yield was no better than with TMSOTf. A typical modified procedure is as follows:

7-ACA (18.4 mM) in dry CH_2Cl_2 (50 ml) was stirred with N-ethylbenzaldimine (92 mM), and TIPSOTf (92 mM) added over 15 min. After 3 h., 1M HCl (10 ml) and 1M $^nBu_4N^+F^-$ in THF (1 ml) were added. The aqueous phase was separated, washed with CH_2Cl_2 (2 x 20 ml) below 10°C, and the pH was adjusted to 6.7 with NEt_3, followed by addition of p-toluenesulphonic acid (6 g) to pH 1.7. Isopropanol (60ml) was run slowly into the rapidly stirred solution, the pH adjusted to 3.0 with NEt_3, and the solution cooled to 0°C. Addition of a further aliquot of isopropanol (60 ml) dropwise gave a precipitate, which was filtered, washed with acetone (2 x 15 ml) and dried to give EAMACA p-toluenesulphonic acid salt (4.1 g, 52.1% yield, 87% strength by quantitative nmr[11] using maleic acid as internal standard).

Attention was also turned to the nature of the nucleophile in order to test if varying its pKa and steric bulkiness would increase the preference for attack at C-3'. It has been reported[4] that 4-NO_2- (3b) and 4-MeO- (3c) analogues of N-ethylbenzaldimine (3a) give less good results in a TMSI-promoted reaction than (3a). Using TMSOTf, the 4-t-butyl-[12] (3d) and 2-trimethylsilyloxy(5)[12,13] N-ethylbenzaldimine analogues were also slightly inferior to the parent imine (relative yields of 0.9 and 0.8 respectively), whereas the 2,4,6-trimethyl analogue (6)[12,14] gave indications of improvements depending on the work-up (relative yield >1.2).

Other aspects, such as ester leaving groups other than acetate and alternative strong acids e.g. TMS superacids, were investigated without realising further improvements.

In conclusion, a practical, operationally simple procedure, with potential for scaling-up, has been developed for introducing alkylamino groups at C-3' of 7-ACA. The method appears mechanistically distinct from the more usual TMSI based procedures[15].

Table III 2a →2b using various triflate reagents (4.5 eq.) with N-ethylbenzaldimine (4.5 eq.) at 23°C in CH_2Cl_2.

Trialkylsilyl triflate		Me_3Si OTf	$tBuMe_2$ SiOTf	$^iPr_3SiOTf$					$^iPr_3SiOTf$ (2.2eq.) then Me_3SiOTf (2 eq.)
Relative yield (hplc peak area ratio)	Aqueous work –up	1.0	1 0						
	Aqueous work–up+ $^nBu_4N^+F^-$ (molar eq)	1.0	1 0	2.0 (1 1)[c]	2 3 (4.3)[c]	1 8 (1 0)[e]	2.0 f)[c]	2 5 g)	>1.0
EAMACA p–TsOH	Yield[a] crystals %	18.1		30 3	d)	22.3	52	h)	
	Strength[b] %	83		98		92	87		

a) ca. 10% product remained unrecovered in solution

b) determined by nmr using maleic acid as internal standard

c) as a 1M solution in THF

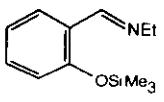
d) emulsification problems

e) as a 10M solution in THF

f) conc. HCl (0.54 molar eq.) and $^nBu_4NF$ (0.05 molar eq.)

g) 40% aq. HF

h) buffering problems in work-up



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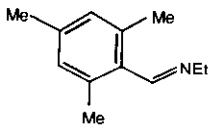

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11. Compound 2b. p-TsOH; mp 169-171°C; ν max 3350-2300, 1770, 1610 cm^{-1}; ^1H nmr (200 MHz; D_2O/DCl) δ 1.4-1.55 (3H,t,J=7Hz), 2.55 (3H,s), 3.2-3.4 (2H,q,J=7Hz), 3.7-4.3 (4H,m), 5.35 (1H,d,J=5Hz), 5.45 (1H,d,J=5Hz), 7.5 (2H,d,J=8Hz), 7.85 (2H,d,J=8Hz).

12. The appropriate aldehyde (60mM) in toluene (100 ml) was refluxed with anhydrous ethylamine (90 mM) using Dean and Stark apparatus. 3Å Molecular sieves were used to remove traces of water, the toluene distilled off and the residue distilled under reduced pressure. Compound 3d; bp 85-88°C/4.5 mmHg; ^1H nmr (90 MHz; $CDCl_3$) δ 1.2-1.4 (12H,m), 3.5-3.8 (2H,q,J=7Hz), 7.4 (2H,d,J=8Hz), 7.65 (2H,d,J=8Hz), 8.2 (1H,s).

13. Compound 5; *to a stirred solution of 2-hydroxybenzaldimine (75 mM) in ether (30 ml)* was added N-trimethylsilylimidazole (82.5 mM) over 10 min. After 30 min., the precipitate was filtered off, the solvent removed, and more imidazole precipitated with cyclohexane. The solution was filtered, evaporated and the residue distilled to give (5) (88% yield), bp 72-76°C/1 mmHg; ^1H nmr (90MHz; $CDCl_3$) δ 0.14 (9H,s), 1.15 (3H,t,J=6Hz), 3.5 (2H,q,J=6Hz), 6.6-7.3 (complex), 7.82 (1H,dd,J=2.5 and 8Hz), 8.55 (1H,s).

14. Compound 6; bp 174-181°C/0.6 mmHg; ^1H nmr (90MHz; $CDCl_3$) δ 1.2-1.4 (3H,t,J=7Hz) 2.25 (3H,s), 2.3 (6H,s), 3.5-3.8 (2H,q,J=7Hz), 6.8 (2H,s), 8.6 (1H,s).

15. This difference is emphasised by the fact that TIPSI gives poorer results when replacing TMSI in contrast to the improvements seen when TIPSOTf replaces TMSOTf.

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