Tetrahedron Letters, Vol.32, No.43, pp 6207-6210, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF NOVEL CEPHEM-4-KETONES. A NEW SERIES OF HUMAN LEUKOCYTE ELASTASE INHIBITORS

Marco Alpegiani, Pierluigi Bissolino, Ettore Perrone,*
Giuseppe Cassinelli and Giovanni Franceschi

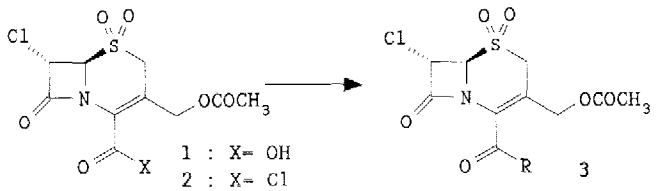
Farmitalia Carlo Erba, Research & Development, via dei Gracchi 35, 20146 Milan, Italy

Keywords:
Cephalosporins; Ketones, preparation of; α-Bromosulphones, preparation and reactivity; Protease inhibitors; Human leukocyte elastase (HLE).

Abstract: Alkylation of cephem-4-carbonyl chlorides at the sulphide or sulphone oxidation level with Grignard reagents, stannanes and cuprates is described. Radical or ionic bromination of the 3-methylcephem-4-ketone 8, followed by displacement with heterocyclic thiols, provides an entry to 3'- and 2-thiosubstituted derivatives, which are new potent inhibitors of HLE.

In the last 30 years chemical manipulation of natural cephalosporins has been intensively carried out with the aim of obtaining new antibacterial agents.[1] Recently, however, modified cephalosporin esters and amides have been found to be potential anti-inflammatory agents in pathologies in which human leukocyte elastase (HLE) is implicated.[2] They lack the classical 7β-acylamino chain and the free carboxyl at C-4, structural prerequisites for antibacterial activity. We have investigated the classes of cephem 4-thioesters[3] and cephem 4-ketones and found that some representatives are very potent inhibitors of HLE. We wish here to report on the synthesis and reactivity of the cephem-4-ketones.

Scanty reports in the literature deal with the introduction of a ketonic function in position 4 of the cephem skeleton; most of them rely on the reaction of cephem-4-carbonyl chlorides with diazomethane to afford 4-(diazoacetyl)cephems, and subsequent transformation of the diazo group.[4] Needing a method that would allow the introduction of different alkyl or aryl residues, we examined the reaction of cephem-4-carbonyl chlorides with Grignard reagents, stannanes and cuprates. 7α-Chlorocephalosporanic acid sulphone 1, whose esters and amides had been reported to be particularly potent inhibitors, was first chosen as a substrate (Scheme 1). Thus when crude acid chloride 2, obtained by treatment

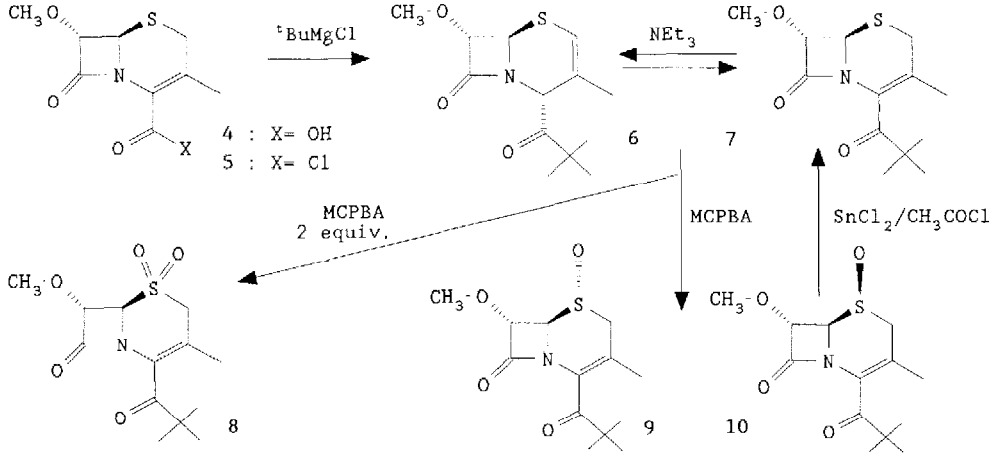


a, R= Bu^t
b, R= CH_2CH_3
c, R= Ph
d, R= CH_2Ph
e, R= (Z)-CH=$CHCH_3$
f, R= H

Scheme 1

of 1 with oxalyl chloride (cat. DMF, THF, 2 h at 0°C), was treated with the Grignard reagents RMgCl (R= *tert*-butyl, ethyl, phenyl, benzyl) in the presence of copper(I) iodide (2 mol equiv. each; THF, -70°C to -40°C, 30 min), the corresponding ketones 3a~d[5] were obtained, albeit in low yields (10-20%). Further, 2 was allowed to react with allyltributyltin and with tributyltin hydride (C_6H_6-CH_2Cl_2 1:1, r.t.). With the former reagent the (*Z*)-propenyl derivative 3e was the main isolated product (30% yield), while with the latter the somewhat unstable aldehyde 3f could be obtained in fair yield (62%).

The intrinsic reactivity of the cephem skeleton, further labilized by the chlorine atom α to the β-lactam carbonyl, the electron withdrawing acetoxy group at C-3' and the sulphonyl moiety at position 1, accounts for the poor yields in the reaction of 2 with Grignard reagents. Thence, a sequence was planned which entailed the Grignard reaction prior to sulphur oxidation (Scheme 2). We focussed our attention on the preparation of cephem 4-*tert*-butyl ketones, which exhibited an optimal compromise between chemical stability and inhibitory properties.[6] For the same reason, 7α-methoxycephems were preferred to their chloro analogues. In particular, ketone 8 was envisaged as a valuable synthetic target. Thus acid 4, easily prepared in one step from 7-ADCA,[7] was converted



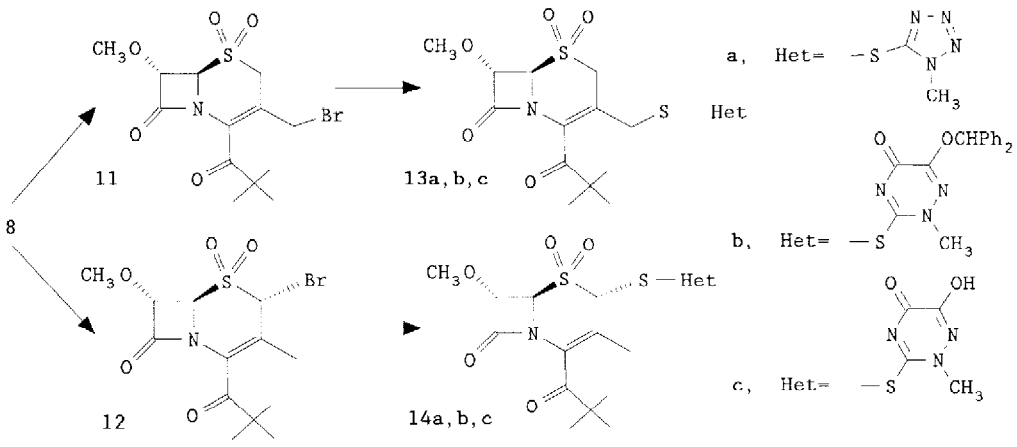
Scheme 2

into its acid chloride 5 with oxalyl chloride. Treatment of 5 with *tert*-butylmagnesium chloride under the afore mentioned conditions gave an inseparable mixture of Δ^2 and Δ^3 cephem ketones 6, 7 in moderate yield. Eventually, oxidation of the crude reaction mixture with excess 4-chloroperoxybenzoic acid (CH_2Cl_2, 6 h) afforded the crystalline sulphone 8. The alkylation of 5 could be performed, more reproducibly, using lithium phenylthio(*tert*-butyl)cuprate[8] (1.2 mol equiv., THF, -70°C, 1 h). Following exposure to MCPBA, 8 was obtained in acceptable overall yields (35-40% from 4).

Mono-oxidation of the mixture 6,7 (MCPBA, 1 mol eq; 0°C, 30 min) allowed, after aqueous work-up, the isolation of sulphoxides 9 and 10 (45:55 ratio), easily separable by silica gel chromatography. The configuration at sulphur of oxides 9 and 10 was attributed on the basis of ^{1}H nmr considerations. In analogy to what observed with cephem-4-esters,[9] the β-sulphoxide 10 shows a long-range coupling between H_6 and $H_{2\alpha}$, which is absent in the spectra of the corresponding α-sulphoxide 9 and sulphide 7. The same long-range coupling is present in all of the sulphones, the 4-ketones 3a~f and 8 included. Its

origin and significance for conformational studies is reported elsewhere.[10] To complete the above picture, the sulphoxide **10** was cleanly reduced by the $SnCl_2/CH_3COCl$ method[11] (CH_3CN-DMF 4:1, 30 min, 70%) to the pure Δ^3 sulphide **7**, and isomerization of the latter to the corresponding Δ^2 cephem-4-ketone in the presence of NEt_3 (5 mol equiv., $CDCl_3$) was monitored by ^1H nmr. The Δ^3: Δ^2 ratio was 6:1 after 3 days and 1:1 after one month.

Sulphone **8** was amenable to functionalization both at C-2 and at C-3', as outlined in Scheme 3. Radical bromination (NBS, cat. AIBN, CCl_4, 5 h at reflux) mainly occurred at



Scheme 3

C-3' to give **11** (60-65%), whose reaction with 5-mercapto-1-methyl-1,2,3,4-tetrazole (MMT) or 6-benzhydryloxy-2,5-dihydro-5-mercapto-5-oxo-triazine[12] in the presence of NEt_3 (CH_3CN, 10 min) uneventfully afforded the respective thioethers **13a,b**. The 2-bromo cephem **12**, a by-product in the radical bromination of **8**, was exclusively produced when **8** was brominated under ionic conditions with stoichiometric amounts of NBS and NEt_3 (CH_2Cl_2, 5 min). Quite unexpectedly, **12** underwent smooth displacement with the afore-mentioned heterocyclic thiols, cleanly yielding **14a,b** (~70-80%). This result is remarkable for the following reasons: *i*, the inertness of α-sulphonyl compounds to SN2 reactions is well documented;[13] *ii*, the 2-halocephem sulphoxides were reported to be resistant to nucleophilic displacements, in contrast to the corresponding cephem sulphides;[14] *iii*, the cephem 4-*tert*-butyl ester analogue of **12** proved reluctant to reaction with MMT, reduction of the bromo atom occurring in place of substitution. The configuration at C_2 of compounds **12** and **14** was provisionally assigned as *S* and *R*, respectively, since the absence of any H_6-H_2 coupling suggests that the latter proton is β-oriented.[10,15] We are trying to elucidate whether the formation of **14a,b** from the bromo-ketone **12** is the result of a straightforward displacement or a two-step sequence involving prior attack of the thiol on the bromo atom and subsequent reaction of the cephem C-2 carbanion on the resulting sulphenyl bromide.

Mild acidic treatment (10% TFA in CH_2Cl_2) of the benzhydryl derivatives **13b** and **14b** smoothly afforded the water-soluble products **13c** and **14c**. In preliminary *in vitro* tests,[6,16] the cephem 4-ketones **3a-e**, **13a-c**, **14a-c** were found to be potent inhibitors of HLE, with distinct advantages over the previously reported cephem 4-esters and amides. Full data on their inhibitory properties and protective effects against elastase-induced lung damage in animal models will be reported in due time.

REFERENCES AND NOTES

1. Kukolja,S.; Chauvette,R.R. Cephem Antibiotics Prepared by Modification at the C-3 Position. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R.B; Gorman M. Eds.; Academic Press: New York 1982; pp. 93-198; Webber,J.A.; Wheeler,W.J. Antimicrobial and Pharmacokinetic Properties of Newer Penicillins and Cephalosporins. *Ibidem*; pp. 371-436.
2. Shah,S.K.; Brause,K.A.; Chandler,G.O.; Finke,P.E.; Ashe,B.M.; Weston,H.; Knight,W.B.; Maycock,A.L.; Doherty,J.B. *J. Med. Chem.* **1990**, *33*, 2529-2535, and references therein.
3. Alpegiani,M. *et al.*, manuscript in preparation.
4. Jen,T.; Dienel,B.; Frazee J.; Weisbach,J. *J. Med. Chem.* **1972**, *15*, 1172-1174; Domiano,P.; Nardelli,M.; Balsamo,A.; Macchia,B.; Macchia,F.; Meinardi,G. *J. Chem. Soc., Perkin Trans.2* **1978**, 1082-1087.
5. ^{1}H nmr (ppm; $CDCl_3$, 200 MHz): **3a**, δ 1.28(9H,s), 2.09(3H,s),3.74(1H,d,J=18.1Hz), 3.99(1H,br d,J=18.1Hz), 4.40 and 4.48(2H,each d,J=13.4Hz), 4.84(1H,dd,J= 1.5,1.7 Hz), 5.36(1H,d,J=1.7Hz); **7**, δ 1.23(9H,s), 1.72(3H,d,J=1.1Hz), 3.01(1H,d,J=17.1 Hz), 3.51(3H,s), 3.53(1H,dq,J=1.1,17.1Hz), 4.48 and 4.68(2H,each d,J=1.8Hz); **8**, δ 1.25(9H,s), 1.69(3H,br s), 3.53(1H,d,J=18.1Hz), 3.54(3H,s), 3.93(1H,br d,J=18.1 Hz), 4.64(1H,dd,J=1.5,1.7Hz), 5.16(1H,d,J=1.7Hz); **9**, δ 1.25(9H,s), 1.74(3H,d,J= 1.3Hz), 3.53(1H,dq,J=1.3,16.2Hz), 3.56 and 3.58(each 3H,s), 3.79(1H,d,J=16.2Hz), 4.36 and 4.91(2H,each d,J=1.8Hz); **10**, δ 1.29(9H,s), 1.74(3H,s), 3.27(1H,br d,J= 18.0Hz), 3.49(1H,d,J=18.0Hz), 3.57(3H,s), 4.32(1H,dd,J=1.8,2.0Hz), 4.98(1H,d,J= 2.0 Hz); **11**, δ 1.29(9H,s), 3.54(3H,s), 3.59(1H,d,J=17.8Hz), 3.79 and 3.88(1H,each d,J=11.4Hz), 4.24(1H,br d,J=17.8Hz), 4.77(1H,dd,J=1.7,1.9Hz), 5.18(1H,d,J=1.9Hz); **12**, δ 1.26(9H,s), 1.82(3H,s), 3.57(3H,s), 4.88(1H,s), 5.15 and 5.31(1H,each d,J= 1.9Hz); **13c**, δ 1.27(9H,s), 3.56(3H,s), 3.63 and 4.17(1H,each d,J=13.8Hz), 3.75(3H, s), 3.63 and 4.08(1H,each d,J=17.8Hz), 4.76(1H,br s), 5.18(1H,d,J=1.1Hz); **14a**, δ 1.25(9H,s), 1.92,3.55 and 4.09(each 3H,s), 4.98(1H,s), 5.10 and 5.18(1H,d,J=1.9Hz)
6. Bissolino,P.; Alpegiani,M.; Perrone,E.; Orezzi,P.; Cassinelli,G.; Franceschi,G. *European Patent Application* 337,704 (18.10.89).
7. Alpegiani,M.; Bissolino,P.; D'Anello,M.; Rivola,G.; Borghi,D.; Perrone,E., accompanying paper.
8. Posner,G.H.; Brunelli,D.J.; Sinoway,L. *Synthesis* **1974**, 662-663.
9. Demarco,P.V.; Nagarajan,R. Physical-Chemical Properties of Cephalosporins and Penicillins. In *Cephalosporins an Penicillins. Chemistry and Biology"*, Flynn,E.H. Ed.; Academic Press: New York 1972; pp. 311-369.
10. Borghi,D.; Alpegiani,M.; Bissolino,P.; Perrone,E. *Gazz. Chim. Ital.*, in press.
11. Kaiser,G.V.; Cooper,R.D.G.; Koehler,R.E.; Murphy,C.F.; Webber,J.A.; Wright,I.G.; Van Heyningen,E.M. *J. Org. Chem.* **1970**, *35*, 2430-2433.
12. Branch,C.L.; Basker,M.J.; Finch,S.C.; Guest,A.W.; Harrington,F.P.; Kaura,A.C.; Knott,S.J.; Milner,P.H.; Pearson,M.J. *J. Antibiotics* **1987**, *50*, 646-651.
13. Bordwell,F.G.; Jarvis,B.B. *J. Org. Chem.* **1968**, *33*, 1182-1185; Loeppky,R.N.; Chang,D.C.K. *Tetrahedron Lett.* **1968**, 5415-5418; Paquette,L.A. *J. Amer. Chem. Soc.* **1964**, *86*, 4085-4089, and references therein.
14. Torii,S.; Tanaka,H.; Saitoh,N.; Siroi,T.; Sasaoka,M.; Tada,N.; Nokami,J. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2185-2186.
15. Cowley,B.R.; Humber,B.C.; Laundon,B.; Long,A.G. *Tetrahedron* **1983**, *39*, 337-342.
16. Bissolino,P.; Alpegiani,M.; Perrone,E.; Orezzi,P.; Cassinelli,G.; Franceschi,G. *U.K. Patent Application*, dep. 8928373.3 (15.12.1989).

(Received in UK 4 April 1991)