SYNTHESIS OF NOVEL FLUORINE-CONTAINING CEPHALOSPORINS

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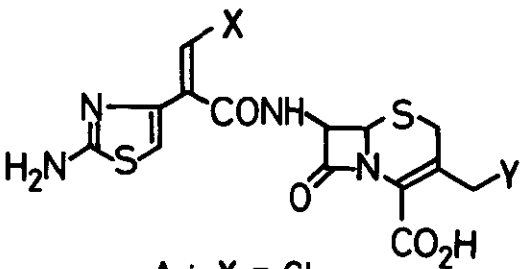
Abstract - Cephalosporins with (E)- and (Z)-7β-[2-(2-aminothiazol-4-yl)-4,4,4-trifluoro-2-butenamido] side chain were synthesized. Of these, the cephalosporin 12e having pyridiniomethyl group at the 3-position exhibited excellent activity against most of microorganisms tested.

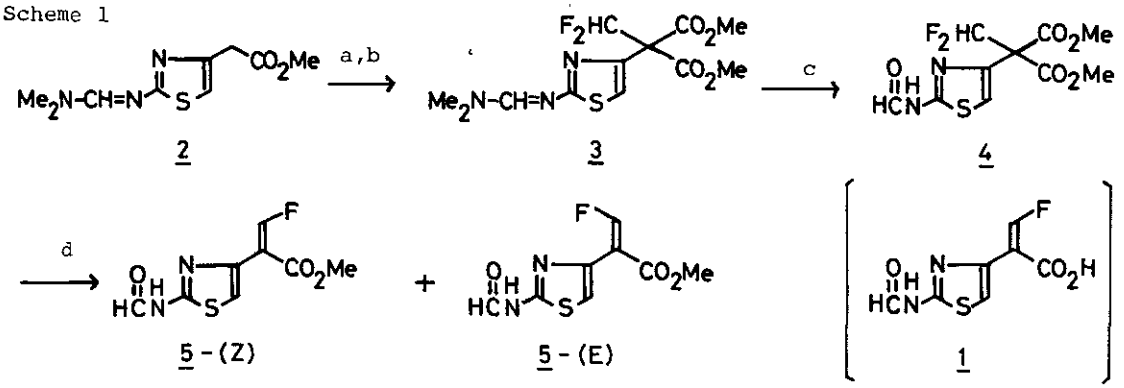
As a part of our program aimed at the research and development of novel cephalosporin antibiotics, we have synthesized a new class of cephalosporins (formula A) possessing (Z)-2-(2-aminothiazol-4-yl)-3-chloro-2-propenamido group at the 7-position in the cephem nucleus.[1] They showed an excellent activity of broad spectrum against microorganisms, as well as good stability to various types of β-lactamases.[2] Substitution of the chlorine of these antibiotics with fluorine or trifluoromethyl will be much more interesting due to their high lipophilicity and also in view of their mimic effect to hydrogen analogues.[3] This paper describes the synthesis of trifluoromethyl substituted cephalosporins (formula C) and their antibacterial activities, as well as the attempted synthesis of the fluorine analogue B.



A : X = Cl
B : X = F
C : $X = CF_3$

At first, our efforts were focused on the synthesis of the fluorine containing side chain acid (1). (Scheme 1)

Scheme 1

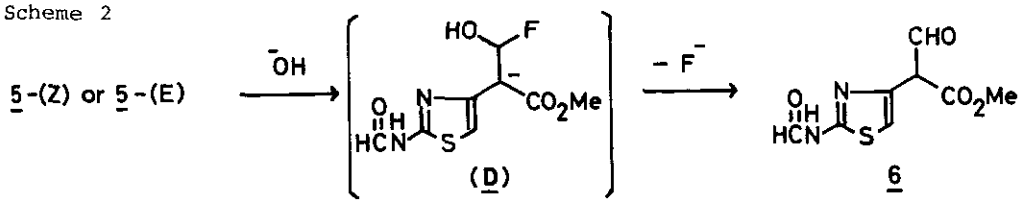


a)NaH-$(MeO)_2CO$, DMF b)$CHClF_2$ c)HCO_2H-Ac_2O d)LiI-DMF, 160°C

Treatment of methyl 2-[2-(N,N-dimethylaminomethylene)aminothiazol-4-yl]acetate (2)[1] with sodium hydride in N,N-dimethylformamide (DMF) in the presence of dimethyl carbonate, followed by addition of chlorodifluoromethane[5] at 0°C, gave dimethyl malonate derivative 3[4] in 46% yield. Thus both methoxycarbonylation[6] and difluoromethylation[7] were achieved in one pot reaction. After conversion of N,N-dimethylaminomethylene compound 3 into formyl derivative 4[4] (88%), dealkoxycarbonylative elimination[8] of HF from the resulting 4 with lithium iodide in DMF[9] gave 3-fluoro-2-propenoates 5-(Z)[10] and 5-(E)[11] in 14 and 52% yields, respectively. Their configurations were assigned on the basis of ^{1}H-nmr spectra and ^{13}C - H coupling constants.[12]

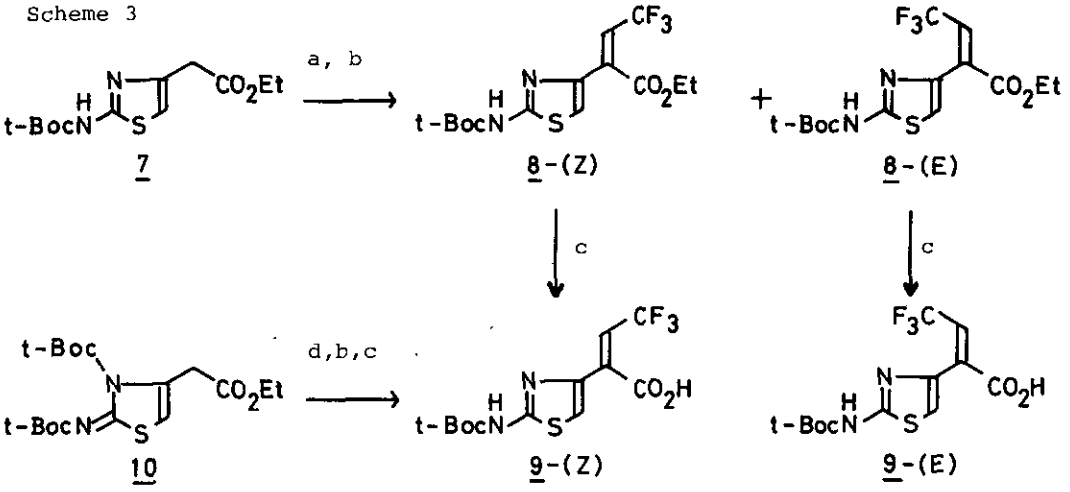
Attempted alkaline hydrolysis of ester 5-(Z) under various reaction conditions gave methyl 3-oxo-2-(2-formylaminothiazol-4-yl)propanoate (6)[1] and no trace of 1. Similar treatment of 5-(E) resulted to give the same product 6. These results were in contrast with the behavior of chloromethylene derivatives which underwent normal alkaline hydrolysis to afford the corresponding (E)- and (Z)-carboxylic acids.[1] These phenomena[13] seem to be ascribable to the strong inductive effect[14] of fluorine atom which stabilizes the β-anion in the intermediate (D).(Scheme 2)

Scheme 2



Accordingly, we have designed the synthesis of carboxylic acids 9 having trifluoromethyl group which is expected to improve the biological activity[15] and does not behave as a leaving group.

Scheme 3

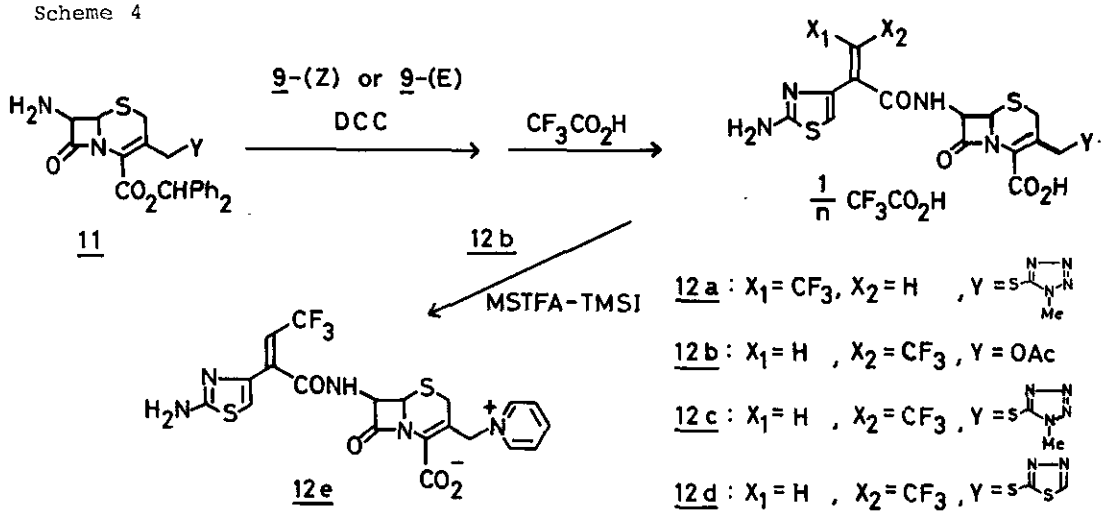


a)NaH, THF-DMF b)CF_3CHO c)NaOH d)n-BuLi, THF

Aldol condensation of 7 with trifluoroacetaldehyde[16] in the presence of sodium hydride, followed by chromatographic separation, gave 8-(Z)[4] and 8-(E)[4] in 10 and 15% yields, respectively. Hydroylsis of 8-(E) proceeded smoothly at room temperature to afford 9-(E)[17] in 96% yield. However, 8-(Z) was intact under the above hydrolysis conditions and necessitated heating at 50°C to give 9-(Z)[18] in 90% yield. Alternatively, we used ethyl 2-(2-t-butoxycarbonylimino-3-t-butoxycarbonyl-4-thiazolin-4-yl)acetate (10)[19] as the starting material. After similar aldol condensation of 10 with trifluoroacetaldehyde, the crude residue was treated with aqueous NaOH solution at room temperature to hydrolyze ester 8-(E), and the remaining ester 8-(Z) was then hydrolyzed by heating at 60°C to afford 9-(Z) in 45% overall yield. (Scheme 3)

Finally, we synthesized the novel cephalosporins 12(a-d)[20] by the coupling reaction of 9 with 7β-aminoceph-3-em-4-carboxylates 11 possessing typical substituents at the 3-position, followed by subsequent removal of the t-butoxycarbonyl and benzhydryl groups. In addition, nucleophilic substitution of the acetoxy group in 12b with pyridine was performed by using N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) - trimethylsilyl iodide (TMSI) method[21] to afford the pyridinium compound 12e[22] in 11% yield.[23] (Scheme 4)

Scheme 4



In the Table, the minimum inhibitory concentrations (MIC) of the cephalosporins 12(a-e) against several microorganisms are summarized and compared with those of cefotaxime (CTX).

Table : Antibacterial activity (MIC μg/ml) of fluorine-containing cephalosporins

Comp. No.	*S. aureus* FDA 209P JC-1	*B. subtilis* ATCC 6633	*E. coli* NIHJ JC-2	*S. typhi* 901	*K. pneumoniae* PCI 602	*P. vulgaris* OX 19	*P. aeruginosa* IFO 3445
12a	3.125	3.125	25	12.5	0.20	0.20	>100
12b	1.56	0.78	0.39	0.78	≦0.025	≦0.025	>100
12c	1.56	1.56	0.78	0.78	≦0.025	≦0.025	>100
12d	0.78	0.78	0.78	0.78	≦0.025	≦0.025	>100
12e	0.39	0.39	0.39	0.39	≦0.025	≦0.025	12.5
CTX	3.125	0.39	0.10	1.56	≦0.025	≦0.025	25

The cephalosporins 12(a-e) showed higher antibacterial activity against S. aureus than CTX. The (Z)-isomer 12c exhibited higher activity than the corresponding (E)-isomer 12a against gram-positive and gram-negative bacteria. A similar tendency was observed with chloromethylene[1] and methoxyimino cephem derivatives.[24] The activity of the pyridinium compound 12e was significantly higher than those of the acetoxymethyl derivative 12b, the other heteroaromatic thiomethyl derivatives 12c, d, and CTX against most of the microorganisms tested, especially against S. aureus.

As a result of our investigations, we have succeeded in synthesizing novel fluorine-containing cephalosporins (C) and found that the trifluoromethyl substituted methylene moiety is associated with the potent antibacterial activities.

ACKNOWLEDGMENTS

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2. D. Tunemoto, T. Kobori, K. Nishide, K. Kondo, T. Toshioka, M. Takanashi, A. Ohno, and S. Goto, 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, New Orleans, La, 1986, Abstract, 1302.
3. I. Kumadaki, J. Synth. Org. Chem. Jpn., 1984, 42, 786 ; 'Biomedicinal Aspects of Fluorine Chemistry', ed. by R. Filler and Y. Kobayashi, Kodansha Ltd., Tokyo, 1982.
4. For these compounds correct elemental analyses and spectroscopic data are in accordance with the structures suggested.
5. P. Bey, J. Fozard, J. M. Lacoste, I. A. McDonald, M. Zreika, and M. G. Palfreyman, J. Med. Chem., 1984, 27, 9 and references cited therein.
6. Ethoxycarbonylation of ethyl 2-[2-(N,N-dimethylaminomethylene)aminothiazol-4-yl]acetate with NaH-$(EtO)_2CO$ in DMF gave diethyl [2-(N,N-dimethylaminomethylene)aminothiazol-4-yl]malonate in 77% yield. On the other hand, ethyl 2-[2-(t-butoxycarbonyl)aminothiazol-4-yl]acetate gave the corresponding ethoxycarbonylated product in 11% yield under the same reaction conditions. Thus, the protection of two protons of amino group in alkyl 2-(2-aminothiazol-4-yl)acetate is desirable to this alkoxycarbonylation.

7. Difluoromethylation of diethyl [2-(N,N-dimethylaminomethylene)aminothiazol-4-yl]malonate described above with NaH-$CHClF_2$ in THF-DMF (1:2) at room temperature gave diethyl difluoromethyl[2-(N,N-dimethylaminomethylene)aminothiazol-4-yl]malonate in 50% yield.

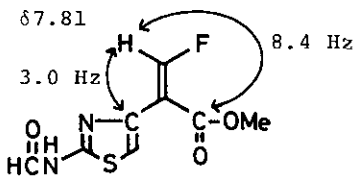
8. The reactions of 4 with KOH-MeOH, t-BuOK-DMSO, or Me_3SiI gave unsuccessful results.

9. A. P. Krapcho, Synthesis, 1982, 805, 893 and references cited therein.

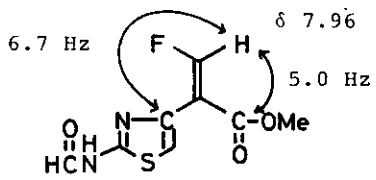
10. 5-(Z) : mp 159-160°C (AcOEt) . IR (KBr); ν 3300, 1695(sh), 1690, 1550, 1260 cm^{-1}. ^{1}H-NMR(DMSO-d_6); δ 3.83(s,3H), 7.33(s,1H), 7.81(d,J_{F-H} = 80 Hz), 8.52(s,1H), 12.41(br s,1H,NH). ^{19}F-NMR(DMSO-d_6:$CFCl_3$ standard); 115.5 ppm(d,J_{F-H} = 80 Hz). ^{13}C-NMR (DMSO-d_6); 52.3, 112.0, 114.6, 140.1, 155.1, 156.4, 159.8, 163.7 ppm. MS m/z (rel intensity); 230(M^+,51), 203(10), 202(100), 199(11), 171(15), 170(46), 151(19), 150(62), 115(12), 101(20), 97(15), 59(14), 57(56), 45(24), 43(11), 15(28). Anal. Calcd for $C_8H_7FN_2O_3S$: C;41.74, H;3.06, N;12.17. Found: C;42.03, H;3.00, N;11.94.

11. 5-(E) : mp 143-145°C (AcOEt) . IR (KBr); ν 3350, 1720, 1700, 1560, 1315 cm^{-1}. ^{1}H-NMR (DMSO-d_6) ; δ 3.75(s,3H), 7.41(s,1H), 7.96(d,J_{F-H} =78 Hz,1H), 8.51(s,1H), 12.44(br s,1H,NH). ^{19}F-NMR (DMSO-d_6 : $CFCl_3$ standard); 110.0 ppm(d,J_{F-H} = 78 Hz). ^{13}C-NMR(DMSO-d_6); 52.2, 114.2, 115.0, 138.3, 155.5, 158.8, 159.6, 165.1 ppm. MS m/z (rel intensity); 230(M^+,29), 203(10), 202(100), 170(32), 151(17), 150(56), 101(16), 97(15), 69(11), 59(14), 57(52), 45(26), 43(11). Anal. Calcd for $C_8H_7FN_2O_3S$: C;41.74, H;3.06, N;12.17. Found: C;41.77, H;3.00, N;12.18.

12. The chemical shifts of vinylic protons and ^{13}C-H coupling constants are as follows:



5-(Z)



5-(E)

13. There is a precedent for this type of reaction: S. Kogure, H. Nakai, and M. Kurono, Prostaglandins, 1979, 18, 737.

14. R. D. Chambers, 'Fluorine in Organic Chemistry', John Wiley & Sons, New York, 1973, p.64.

15. For recent papers of synthetic pyrethroid analogs having trifluoromethyl group in place of chlorine atom see: M. Fujita and T. Hiyama, Tetrahedron Lett., 1986, 27, 3655 and references cited therein.

16. D. G. Hooper, L. F. Loucks, and M. T. H. Liu, J. Chem. Educ., 1975, 52, 131.

17. 9-(E): mp 182°C(dec). ^{1}H-NMR (acetone-d_6); δ 1.51(s,9H), 5.2-6.4(br s,NH, CO_2H,2H), 6.84(br q,J_{F-H} = 8.5 Hz,1H), 7.24(br s,1H). ^{19}F-NMR (acetone-d_6) ; 57.1 ppm(br d,J_{F-H} = 8.5 Hz). MS m/z (rel intensity); 282(1), 238(10), 194(18), 151(10), 125(20), 59(16), 57(39), 56(53), 55(14), 44(100), 41(85), 39(33). Anal. Calcd for $C_{12}H_{13}F_3N_2O_4S$: C;42.60, H;3.87, N;8.28. Found : C;42.36, H;3.74, N;8.00.

18. 9-(Z): ^{1}H-NMR (acetone-d_6); δ 1.55(s,9H), 5.9-7.1(br s, NH, CO_2H,2H), 6.52 (br q,J_{F-H} = 8.5 Hz,1H), 7.31(br s,1H). MS m/z (rel intensity); 338(M^+,5), 282(6), 238(31), 220(10), 194(17), 151(34), 125(31), 82(9), 69(9), 59(29), 58(16), 57(100), 56(14), 45(25), 44(21), 43(12), 41(67), 39(24).

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20. 12a : Yield 25%. IR (KBr); ν 1785 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 3.6-3.9(AB,2H), 4.69(s,3H), 4.27(AB d,J = 13.4 Hz,1H), 4.42(AB d,J = 13.4 Hz,1H), 5.16(d, J = 4.5 Hz,1H), 5.75(dd,J = 8.0 and 4.5 Hz,1H), 6.32(q,J_{F-H} = 8.5 Hz,1H), 6.81(s,1H), 7.2(br s,2H,NH_2), 9.50(br d,J = 8.0 Hz,1H,NH). ^{19}F-NMR (DMSO-d_6 : $CFCl_3$ standard) 55.5 ppm(d,J_{F-H} = 8.5 Hz,CF_3), 73.5 ppm(s,CF_3CO_2H) (3:1). n = 3.

12b : Yield 54%. IR (KBr); ν 1780, 1740 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 2.03(s,3H), 3.3-3.8(AB,2H), 4.70(AB d,J = 12.8 Hz,1H), 5.00(AB d,J = 12.8 Hz,1H), 5.18(d, J = 4.8 Hz,1H), 5.81(dd,J = 7.9 and 4.8 Hz,1H), 6.0-8.0(br s,3H,NH_2,CO_2H), 6.29(q,J_{F-H} = 9.0 Hz,1H), 6.71(s,1H), 9.69(d,J = 7.9 Hz,1H,NH). ^{19}F-NMR (DMSO-d_6 : $CFCl_3$ standard) ; 57.5 ppm (d,J_{F-H} = 9.0 Hz,CF_3) and 73.9 ppm (s,CF_3CO_2H)(3:1). n = 3.

12c : Yield 31%. IR (KBr); ν 1785 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.55-3.90(AB,2H), 3.95(s,3H), 4.26(AB d,J = 13.5 Hz,1H), 4.40(AB d, J = 13.5 Hz,1H), 5.19(d, J = 5.0 Hz,1H), 5.83(dd, J = 8.0 and 5.0 Hz,1H), 6.32(q,J_{F-H} = 9.0 Hz,1H), 6.74(s,1H), 7.28(br s,2H,NH_2), 9.76(br d,J = 8.0 Hz,1H,NH). ^{19}F-NMR (DMSO-d_6 : $CFCl_3$ standard); 57.3 ppm (d, J_{F-H} = 9.0 Hz,CF_3) and 73.6 ppm(s,CF_3CO_2H)(5:1). n = 5.

12d : Yield 26%. IR (KBr); ν 1780 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 3.63(AB d,J = 18.0 Hz,1H), 3.78(AB d,J = 18.0 Hz,1H), 4.31(AB d,J = 13.1 Hz,1H), 4.61(AB d, J = 13.1 Hz,1H), 5.20(d,J = 4.5 Hz,1H), 5.82(dd,J = 8.0 and 4.5 Hz,1H), 6.52(q,J_{F-H} = 9.0 Hz,1H), 6.74(s,1H), 7.26(br s,2H,NH_2), 9.58(s,1H), 9.72(br d, J = 8.0 Hz,1H). ^{19}F-NMR (DMSO-d_6:$CFCl_3$ standard); 57.6 ppm (d,J_{F-H} = 9.0 Hz,CF_3) and 73.3 ppm (s,CF_3CO_2H) (6:1). n = 6.

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22. 12e : IR (KBr); ν 1780 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 3.10(AB d,J = 17.8 Hz,1H), 3.53(AB d,J = 17.8 Hz,1H), 5.10(d,J = 5.0 Hz,1H), 5.13(AB d,J = 12.8 Hz,1H), 5.68(AB d,J = 12.8 Hz,1H), 5.69(dd,J = 9.0 and 5.0 Hz,1H), 6.24(q,J_{F-H} = 9.0 Hz,1H), 6.60(s,1H), 7.20(br s,2H,NH_2), 8.15(br t,J = 6 Hz,2H), 8.59(br t,J = 6 Hz,1H), 9.46(br d,J = 6 Hz,2H), 9.60(d,J = 9.0 Hz,1H,NH). ^{19}F-NMR(DMSO-d_6: $CFCl_3$ standard); 57.5 ppm (d,J_{F-H} = 9.0 Hz, CF_3).

23. The crude 12e was subjected to Diaion HP-20 chromatography.

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