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TOTAL SYNTHESIS OF 3-TRIFLUOROMETHYLCEPHALOSPORIN DERIVATIVES

T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto,
M. Nagano and T. Miyadera*
Central Research Laboratories, Sankyo Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo, Japan

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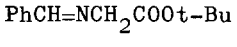
An electron-withdrawing substituent introduced at the 3-position of cephalosporin derivatives facilitates the nucleophilic cleavage of the β-lactam amide bond[1] and as a result enhances their antimicrobial activities.[2] The synthetic chemistry of cephalosporin compounds based on structure-activity relationships has been extensively explored through total synthesis and molecular modifications of naturally occurring cephalosporins and penicillins. With the view of obtaining a highly active cephalosporin antibiotic, our attention was focused on the trifluoromethyl group. Having a greater electron-withdrawing effect than the chlorine atom, the CF_3 group was thought to influence antimicrobial properties of 3-substituted cephalosporins to a greater extent than the chlorine atom.[3]

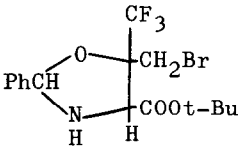
This preliminary report describes the total synthesis of 3-trifluoromethylcephalosporin derivatives involving the reaction of a benzylideneglycine ester (I) with a ketone which may provide a convenient method to prepare key intermediates for a wide variety of penicillin or cephalosporin syntheses.

N-Benzylideneglycine tert-butyl ester (I) was treated with n-butyllithium in tetrahydrofurane(THF) with cooling in a dry ice-acetone bath followed by addition of a solution of 3-bromo-1,1,1-trifluoroacetone in THF. The reaction mixture was quenched with an equimolar amount of AcOH and the resultant oxazolidine (when the ethyl ester was employed, the corresponding oxazolidine was isolated by silica gel column chromatography) was treated with Girard T in MeOH at room temperature to give approximately a 3:1 mixture of two diastereomers

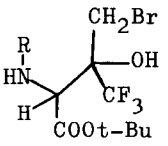
(IIIa and IIIb) in 70% yield. NMR($CDCl_3$) ppm: IIIa, 1.53 (s, t-Bu), 3.19 (bs, NH_2, OH), 3.87 (s, $C\underline{H}_2Br$), 3.95 (q, J=1.2 Hz, $C\underline{H}COO$); IIIb, 1.56 (s, t-Bu), 3.40(bs, NH_2, OH), 3.63, 3.91(AB-q, J=11 Hz, $C\underline{H}_2Br$), 3.89(q, J=1.0 Hz, $C\underline{H}COO$). The two isomers were separated by column chromatography on silica gel eluting with benzene-AcOEt (20:1). Thioformylations of IIIa and IIIb with two mole-equivalents of ethyl thioformate in CCl_4 at room temperature afforded thioamides (IVa and IVb) in 57 and 55% yields, respectively. NMR($CDCl_3$): IVa, 1.53 (s, t-Bu), 3.77, 4.05 (AB-q, J=12 Hz, $C\underline{H}_2Br$), 4.56 (bs, OH), 6.18 (bd, J=9.5 Hz, $C\underline{H}COO$), 8.15 (b, NH), 9.65 (d-d, J=9.5, 1.0 Hz, $C\underline{H}S$); IVb, 1.54 (s, t-Bu), 3.71 (s, $C\underline{H}_2Br$), 5.96 (bd, J=9 Hz, $C\underline{H}COO$), 8.41 (b, NH), 9.65 (d, J=6 Hz, $C\underline{H}S$). Ring closures of IVa and IVb with powdered K_2CO_3 (3 mole-equiv.) in acetone for 15 min at room temperature gave 1,3-thiazines (Va, mp 128° and Vb, mp 165° (decomp.) in 70 and 44% yields, respectively. NMR($CDCl_3$) ppm: Va, 1.53 (s, t-Bu), 3.03 (d-d-d, J=13, 1.2, 1.0 Hz, C_6-H), 3.14 (d, J=13 Hz, C_6-H), 4.19 (d-d, J=1.0, 3.0 Hz, C_4-H), 5.40 (bs, OH), 8.34 (d-d, J=1.2, 3.0 Hz, C_2-H); Vb, 1.48 (s, t-Bu), 2.93 (d-d-d, J=13, 2.5, 1.5 Hz, C_6-H), 3.73 (d, J=13 Hz, C_6-H), 4.62 (d-d, J=2.5, 1.5 Hz, C_4-H), 8.32 (t, J=1.5 Hz, C_2-H). The thiazine Va was treated with NaH in THF with ice-cooling and then with CH_3SO_2Cl followed by cycloaddition reaction with N_3CH_2COCl and Et_3N[4] in THF. The crude product was chromatographed on silica gel, eluting with benzene to give a 15% yield of the trans 7-azido-3-cephem derivative (VII, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100(N_3), 1792 (β-lactam). NMR($CDCl_3$) ppm: 1.58 (s, t-Bu), 3.50 (m, CH_2), 4.70 (s, C_6-H, C_7-H)). Further elution with benzene-AcOEt (10:1) afforded a 70% yield of the 3-mesyloxy derivative (VI, NMR($CDCl_3$) ppm: 1.56 (s, t-Bu), 3.18 (s, OMs), 3.50, 4.18 (AB-q, J=15 Hz, downfield peaks are broad because of long-range coupling with CF_3, CH_2), 4.57 (d, J=1.5 Hz, C_7-H), 4.87 (s, C_4-H), 5.05 (bs, C_6-H). The ratio of VI to VII varies considerably depending upon the reaction conditions. The mesylate VI was quantitatively converted into VII by heating a benzene solution of VI containing excess pyridine at 50°C. The cycloaddition reaction of the isomeric thiazine Vb was also carried out under the same conditions to give VII. The stereochemistry of VI was determined by X-ray crystallographic analysis which also permitted stereochemical assignments of the



(I)

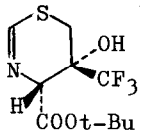


(II)

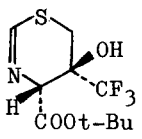


(III) R = H

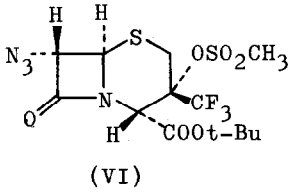
(IV) R = CH=S



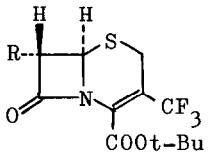
(Va)



(Vb)

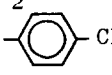


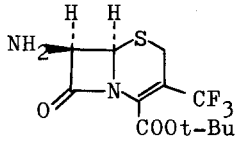
(VI)



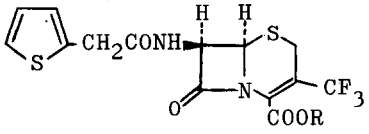
(VII) R = N_3

(VIII) R = NH_2

(IX) R = NO_2  CH=N



(X)



(XI) R = t-Bu

(XII) R = H

diastereomers (III-V). Catalytic hydrogenation of VII over 10% Pd-C in THF in the presence of p-toluenesulfonic acid gave the <u>trans</u> 7-amino derivative (VIII) in a quantitative yield. NMR($CDCl_3$)ppm: 1.55 (s, t-Bu), 2.26 (bs, NH_2), 3.48 (m, CH_2), 4.35 (d, J=2 Hz, C_7-H), 4.60 (d, J=2 Hz, C_6-H). The isomerization of VIII to <u>cis</u> isomer (X, NMR($CDCl_3$)ppm: 1.56 (s, t-Bu), 1.80 (bs, NH_2), 3.46 (m, CH_2), 4.79 (d, J=5 Hz, C_6-H), 4.96 (d, J=5 Hz, C_7-H)) was performed by the method[5] involving the formation of the Li salt of the p-nitrobenzylideneamino derivative (IX) and subsequent protonation. An alternative method was applied more effectively to the <u>trans</u>-<u>cis</u> conversion which will be described in the forthcoming paper. Acylation of X with 2-thiopheneacetyl chloride and N,N-diethylaniline in THF-$ClCH_2CH_2Cl$ at 0°C afforded a 88% yield of the acyl derivative (XI, NMR($CDCl_3$)ppm: 1.51 (s, t-Bu), 3.34, 3.50 (AB-q, J=19 Hz, C_2-H_2), 3.84 (s, $C\underline{H}_2CO$), 4.96 (d, J=5 Hz, C_6-H), 5.85 (d-d, J=5, 9 Hz, C_7-H), 6.29 (d, J=9 Hz, NH), 7.0-7.3 (m, thienyl protons). The tert-butyl of XI was deprotected by treatment in CF_3COOH at room temperature to give the desired <u>dl</u>-7β-[2-(2-

thienyl)acetamido]-3-trifluoromethyl-3-cephem-4-carboxylic acid (XII), mp 213-214° (decomp.) (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1785 (β-lactam). NMR($(CD_3)_2CO$)ppm: 3.59, 3.74 (AB-q, J=18 Hz, C_2-H_2), 3.88 (s, CH_2CO), 5.26 (d, J=5 Hz, C_6-H), 5.95 (d-d, J=5, 9 Hz, C_7-H), 6.8-7.4 (m, thienyl protons), 8.16 (bd, J=8 Hz, NH).

The biological data on XII will be reported elsewhere, together with a number of acyl derivatives including 2-cephem and 7-methoxy derivatives.

The reactions of the benzylideneglycine ester (I) with a variety of ketones and aldehydes are under investigation.

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