SYNTHESIS AND REACTIONS OF C(3)-PROPYN-1'-OL CEPHEM

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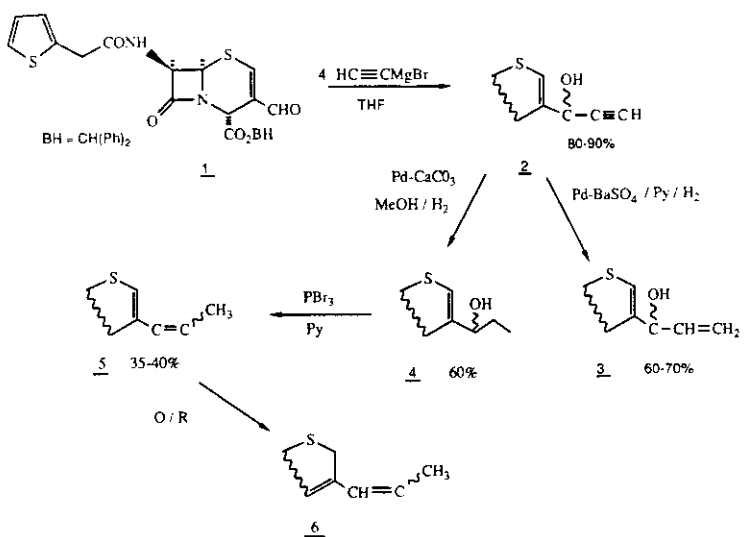
Abstract - Cephalosporin-C(3)-allenes, propenes, acyl pyrazoles, pyrazoles and isoxazoles can be synthesized from the C(3)-propyn-1´-ol cephem 2.

Several years ago we reported the reaction of Grignard reagents with C(3)-formylcephem 1 to give the diastereoisomeric carbinols and their subsequent oxidation to give the corresponding ketone.[1] In this paper we detail the synthesis and some of the chemistry of C(3)-propyn-1´-ol cephem 2.

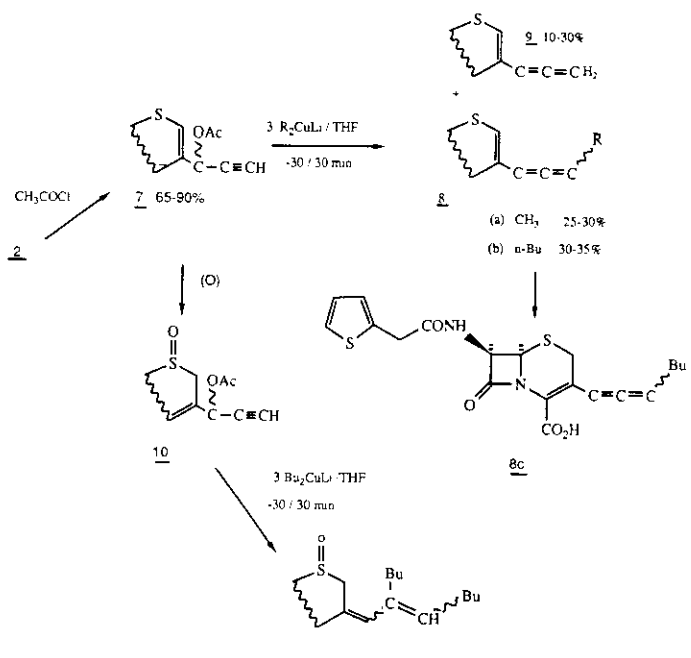
The diastereomeric propyn-1´-ol cephem 2[2] was prepared by dropwise addition of a THF solution of the Δ^2-aldehyde 1, at room temperature, to four equivalents of ethynylmagnesium bromide[3]. After five min the reaction was quenched with excess 20% NH_4Cl, EtOAc was then added, followed by aqueous washing, brine, drying over Na_2SO_4 and evaporation to give 80-90% crude 2.



Reduction of the acetylenic moiety using $Pd\text{-}BaSO_4/Py/H_2$ gave the allylic alcohol 3, while use of $Pd\text{-}CaCO_3/MeOH/H_2$ gave the saturated alcohol 4. Both 3 and 4 can be prepared from 1 using the appropriate Grignard reagent. Treatment of 4 with PBr_3-pyridine or N-methylmorpholine gave the C(3)-propene as an apparent E-Z mixture. Sulfur oxidation (74%) and reduction[4] (89%) gave the Δ^3-propenyl derivatives 6, the major isomer (E) of which was crystalline.[5,6] Workers at Bristol have recently found the C(3)-Z-propenyl-p-hydroxy-phenylglycine adduct (BMY 28100) to be of interest.[7]

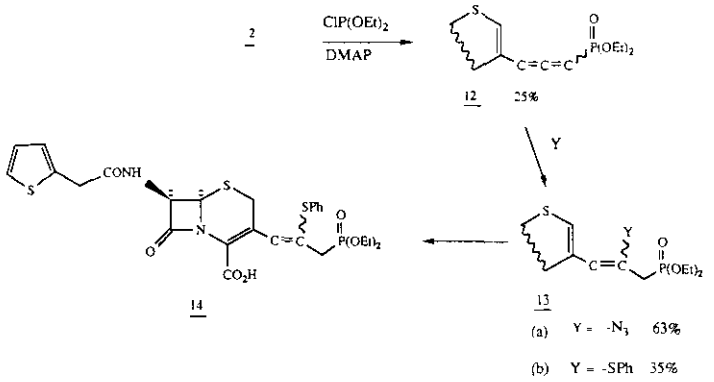
Acylation of 2 with acetyl chloride-N-methylmorpholine gave the diastereoisomeric propargyl acetates 7[8] (65-90%) whose Δ^3-acids exhibit poor microbiological activity. Other C(3)-secondary acetates have been prepared [1a,9] and shown to have poor activity because of rapid acetate hydrolysis to give the carbonium ion followed by subsequent lactone formation[9].

Reaction of the propargyl acetates 7 with lithium dialkylcuprates[10] (Me, n-Bu) afforded the substituted diastereomeric allenes 8[11] (R=Me, n-Bu) and the "reduced" allene 9[12] in only moderate yield with no evidence for the alkylated acetylene.[13]



The butyl allene 8b was converted to its Δ^3-cephem isomer and the benzhydryl ester was cleaved with formic acid to give the corresponding acid 8c, which showed poor gram negative antibacterial activity (see Table I). The addition of excess lithium di-n-butylcuprate to the Δ^3-C(3)-propargyl acetate 10 gave 11 in 35% (two isomers isol. 16%, 19%). This is an apparent result of substituted allene formation followed by 1,6-conjugate addition. We have previously reported the 1,6-conjugate addition of lithium-di-n-butylcuprate to the Δ^3-C(3)-vinylcephem system.[14]

The allene phosphonates 12[15] were prepared from 2 using diethyl chlorophosphite[16]. The corresponding Δ^3-acids showed very poor microbiological activity. Two nucleophiles, NaN_3[17] and PhSH, were added in Michael fashion to 12 to give 13a (63%) and 13b[18] (35%). The latter was converted to the corresponding Δ^3-acids 14, which again showed poor gram negative activity (Table I).

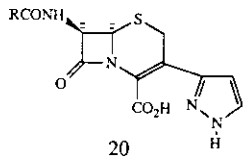


The propyn-1´-ol cephem 2 was cleanly oxidized with chromic acid to the ketone 15[19] (64% overall yield from 1), which undergoes 1,3-dipolar cycloaddition with diazomethane (50%) or diphenyldiazomethane (87%) to give the corresponding acyl pyrazole 16a and 16b. The acetylenic ketone 15 reacts with hydroxylamine[20] to give the isoxazole (60%) 17 and with hydrazine[21] to give the pyrazole 18[22] (55-60%).[23] The microbiological activities of the Δ^3-pyrazoles 20A-D were studied in detail (see Table I).

TABLE I

MIC (μg/ml)

	Staphylococcus						Streptococcus				H. Influ		E. coli			Klebsiella		
	Aureus				Epi		A	pn	D		sens	res						
Strain	X1.1	V41	X400	S13E	270	222	C203	Park	X66	2041	C.L.	76	N10	EC14	TEM	X26	KAE	X68
cephalothin	.25	1	32	2	1	.25	.125	.125	32	32	2	2	16	4	8	1	128	4
8c	.25	1	64	32	4	.25	.015	.03	32	64	32	32	128	128	128	128	128	128
14	1	16	128	128	32	2		.06	128	8	128	128	128	128	128	128	128	128
20A	1	32	64	32	8	2	.06	.06	64	16	32	16	128	128	128	16	128	128
20B	4	32	128	32	64	8	.03	.03	128	4	.125	.06	2	.5	2		16	.5
20C	2	32	64	32	16	4	.125	.125	64	32	32	16	128	32	128	4	128	32
20D	2	32	128	32	32	4	.06	.125	128	64	64	32	128	128	128	8	128	128



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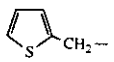
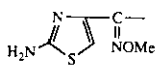
R (20 ONLY)

A

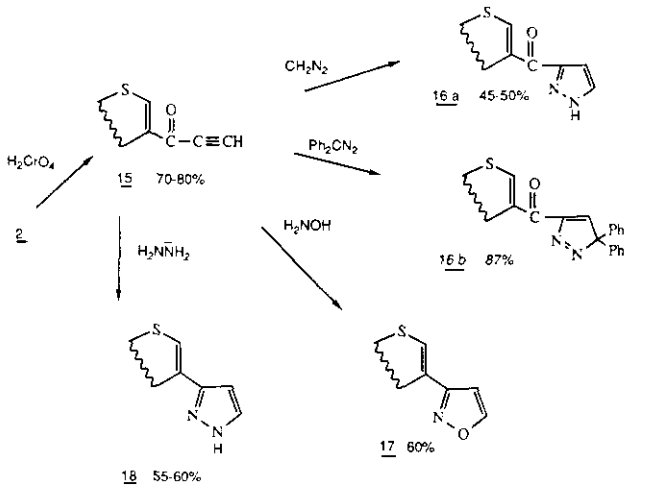


B

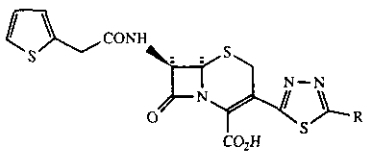


C

D



The C(3)-pyrazole moiety causes substantial loss in gram negative activity. This is a common trait of C(3)-hetero[24] and heteroaromatic[23,25] rings, with the apparent exception of Takeda's[26] C(3)-5-substituted 1,3,4-thiadiazole 19 which is reported to have similar gram positive, but superior gram negative activity when compared to cephalothin.



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2. 2 (4α, 7β, 7aα)-3-(1-Hydroxy-2-propynyl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 544; ir ($CHCl_3$) 3200, 1725 cm^{-1}; nmr ($CDCl_3$) δ 2.40 (d, J=2 Hz, 1, C≡C<u>H</u>), 3.6 (bs, 1, OH), 3.76 (s, 2, thiophene methylene), 4.88 (bs, 1, methine), 5.05 (d, J=4 Hz, 1, H_6), 5.20 (s, 1, H_4), 5.48 (d,d, J=4, 6 Hz, 1, H_7), 6.60 (s, 1, H_2).

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5. 6 (7B)-3-(Z)-1-Propenyl-7-[(2-thienylacetyl)amino]-3-cephem-4-carboxylic acid, diphenylmethyl ester, mp 178-179° C ($PhCH_3$/EtOAc); m/z/ 530; ir ($CHCl_3$) 1775 cm^{-1}; λ ETOH 300 nm ε 7,620; nmr ($CDCl_3$) δ 1.76 (d, J=8 Hz, 3, Me), 3.38, 3.50 (AB, J=16 Hz, 2, C(2)-methylene), 3.85 (s, 2, thiophene methylene), 5.00 (d, J=4 Hz, 1, H_6), 5.76 (d,d, J=4, 8 Hz, 1, H_7), 5.95 (6 peaks, J=6, 16 Hz, 1, C=C<u>H</u>Me), 6.47 (d, J=8 Hz, 1, NH), 6.82 (d, J=16 Hz, 1, -C<u>H</u>=CHMe).

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8. 7 (4α, 7β, 7aα)-3-(1-Acetoxy-2-propynyl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: one isomer crystalline 160-161° C (CH_2Cl_2/hexanes); m/z 586; ir ($CHCl_3$) 3300, 2135, 1780 cm^{-1} nmr ($CDCl_3$) δ 1.82 (s, 3, OAc), 2.37 (d, J=2 Hz, 1, C≡C<u>H</u>), 3.84 (s, 2, thiophene methylene), 5.07 (m, 2, H_6+methine), 5.55 (d,d, J=4, 8 Hz, 1, H_7), 5.94 (s, 1, H_4), 6.40 (d, J=8 Hz, 1, NH), 6.69 (s, 1, H_2).

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11. 8a (4α, 7β, 7aα)-3-(1-2-Butadienyl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 542; ir ($CHCl_3$) 1935, 1770 cm^{-1}; nmr ($CDCl_3$) δ 1.2-1.6 (m, 3, Me), 3.76 (s, 2, thiophene methylene), 4.96 (d, J=4 Hz, 1, H_6), 5.05 (s, 1, H_4), 5.48 (d, d, J=4, 8 Hz, 1, H_7), 5.74 (m, 1, C=CHMe), 6.04 (s, 1, H_2), 6.58 (d, J=8 Hz, 1, NH); ^{13}C nmr ($CDCl_3$) δ center C of allene at 204.67.

    8b (4α, 7β, 7aα)-3-(1,2-Heptadienyl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 584; ir ($CHCl_3$) 1938, 1775 cm^{-1}; nmr ($CDCl_3$) δ 0.6-1.8 (m, 9, Bu), 3.80 (s, 2, thiophene methylene), 4.96 (d, J=4 Hz, 1, H_6), 5.10 (s, 1, H_4), 5.42 (d,d, J=4, 9 Hz, 1, H_7), 5.76 (m, 1, C=CHBu), 6.08 (s, 1, H_2); ^{13}C nmr ($CDCl_3$)δ center C of allene at 202.56.

12. sulfoxide of 9 (7β)-3-(1,2-Propadienyl)-7-[(2-thienylacetyl)amino]-3- cephem-4-carboxylic acid, diphenylmethyl ester-1-oxide: m/z 544; ir ($CHCl_3$) 1920, 1790 cm^{-1}; nmr ($CDCl_3$) δ 3.04, 3.92 (AB, J=18 Hz, 2, C(2) methylene), 3.82 (s, 2, thiophene methylene), 4.44 (s, J=4 Hz, 1, H_6), 5.15 (d, 2, $C=CH_2$), 5.96 (d, d, J=4, 8 Hz, 1, H_7).

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15. 12 (4α, 7β, 7aα)-3-[3-(Diethoxyphosphinyl)-1,2-propadienyl]-7-[(2-thienyl acetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester; m/z 664; ir ($CHCl_3$) 1935, 1780 cm^{-1}; nmr ($CDCl_3$) δ 1.20-1.46 (m, 6, OCH_2CH_3), 3.85 (s, 2, thiophene methylene), 3.84-4.3 (m, 4 OCH_2CH_3), 5.03 (s, 1, H_4), 5.12 (d, J=4 Hz, 1, H_6), 5.53 (d, d, J=4, 8 Hz, 1, H_7), 6.1-6.5 (m, 1, $C=CHP(O)(OEt)_2$), 6.40 (s, 1, H_2).

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18. 13b (4α, 7β, 7aα)-3-[3-(Diethoxyphosphinyl)-2-(phenylthio)-1-propenyl]-7-[(2-thienyl-acetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 774; ir ($CHCl_3$) 1774 cm^{-1}; nmr ($CDCl_3$) δ 1.17-1.50 (m, 6, OCH_2CH_3), 2.0-3.2 (m, 2, $CH_2P(O)$-), 3.80 (s, 2, thiophene methylene), 4.13 (q, J=7 Hz, 4, OCH_2CH_3), 4.82 (s, 1, H_4), 5.25 (d, J=4 Hz, 1, H_6), 5.58 (d, d, J=4, 8 Hz, 1 H_7), 5.80 (m, 1, CH=C).

19. 15(4α, 7β, 7aα)-3-(1-Oxo-2-propynyl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 542; ir ($CHCl_3$) 3290, 2100, 1780, 1625 cm^{-1}; EtOH λ 310 nm ε 13,098; nmr ($CDCl_3$) δ 3.30 (s, 1, C≡CH), 3.78 (s, 2, thiophene methylene), 5.00 (d, J=4, 1, Hz, H_6), 5.37 (d, d, J=4, 8 Hz, 1, H_7), 5.57 (s, 1, H_4), 8.07 (s, 1, H_2).

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22. 18 (4α, 7β, 7aα)-3-(1H-Pyrazol-3-yl)-7-[(2-thienylacetyl)amino]-2-cephem-4-carboxylic acid, diphenylmethyl ester: m/z 556; ir ($CHCl_3$) 1777, cm^{-1}; EtOH λ 273 ε 14,000; nmr ($CDCl_3$) δ 3.78 (s, 2, thiophene methylene), 5.13 (d, J=4 Hz, 1, H_6), 5.53 (d, d, J=4, 8 Hz, 1, H_7), 5.67 (s, 1, H_4), 6.17 (d, J= 2 Hz, 1, C_4 H of pyrazole), 6.58 (s, 1, H_2), 8.7 bs, 1, NH of pyrazole).

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