SYNTHESIS OF C(3)-ALKYL CEPHEMS

Douglas O. Spry* and Anita R. Bhala

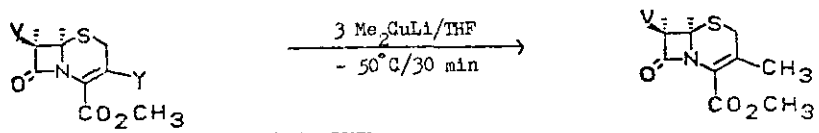
The Lilly Research Laboratories

Eli Lilly and Company

Indianapolis, Indiana 46285, U.S.A.

Abstract - C(3)-n-Butyl and n-hexyl cephems have been prepared by the conjugate addition of the appropriate organocuprate to the C(3)-chloro and C(3)-vinyl cephem.

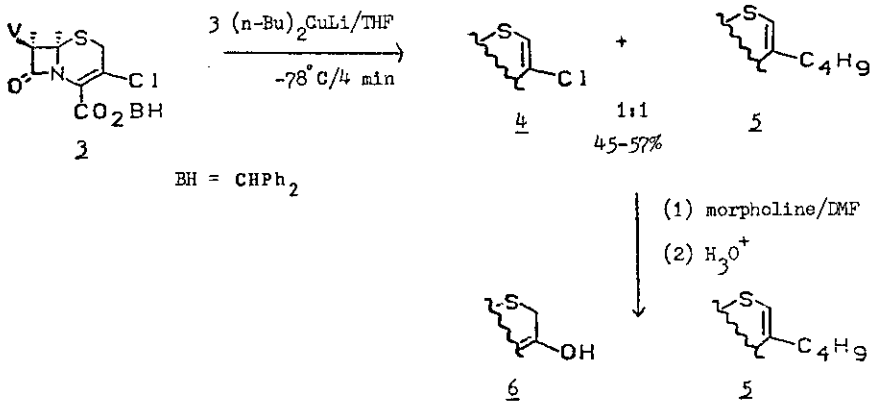
We recently attempted to synthesize C(3)-alkyl cephem derivatives via the reaction of Grignard reagents on C(3)-halo and other C(3)-electron rich cephems.[1] This reaction resulted in S(1)-C(2)-secocephems via a SET (single electron transfer) mechanism. We now report the use of organocuprate reagents to prepare various C(3)-alkyl cephem derivatives. Lithium organocuprates are known to undergo conjugate addition via a SET mechanism to give copper complexes which then undergo an intramolecular rearrangement to give the product.[2] It was anticipated that the difference in the mode of transfer for the R group would result in the desired C(3)-alkyl cephem products. Indeed, the C(3)-chloro cephem 1A reacted with lithium dimethylcuprate to give a 50% yield of the C(3)-methyl compound 2. C(3)-S-Phenyl 1B also reacted with lithium dimethylcuprate to give 28% 2 plus 24% starting material, however, C(3)-OMe gave 39% Δ^2 (isomerization of the double bond) plus 38% starting material, while the C(3)-morpholine-enamine gave 97% starting material. Under these conditions the C(3)-mesylate gave 58% enol, while the C(3)-diethylphosphonate[3] gave 34% starting material.



1	Y	2
A	Cl	50%
B	SPh	28%

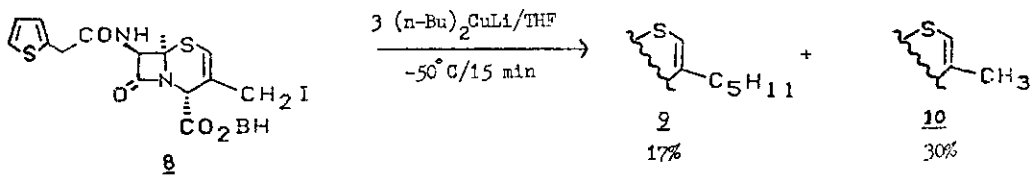
Other esters of V-C(3)-chloro cephem, i.e. benzhydryl and trichloroethyl, work equally as well (39%, 37%), however, p-nitrobenzyl was unacceptable, resulting in decomposition.

Under the conditions described for the conversion of 1 to 2, lithium diphenylcuprate failed to react with 1A, while lithium diallylcuprate gave 37% of the C(3)-hydro derivative, that is the reduced product plus 43% starting material. Lithium di-n-butylcuprate reacted with 3 to give a 47-57% mixture of Δ^2-C(3)-Cl 4 and Δ^2-C(3)-n-butyl 5 (ca. 1:1). This mixture proved very difficult to separate by any means, as were the sulfoxides of 4 and 5. However, the chloro derivative 4 can be converted to the enol 6 via the enamine, thus drastically changing its Rf and allowing easy separation of 5 by silica chromatography.

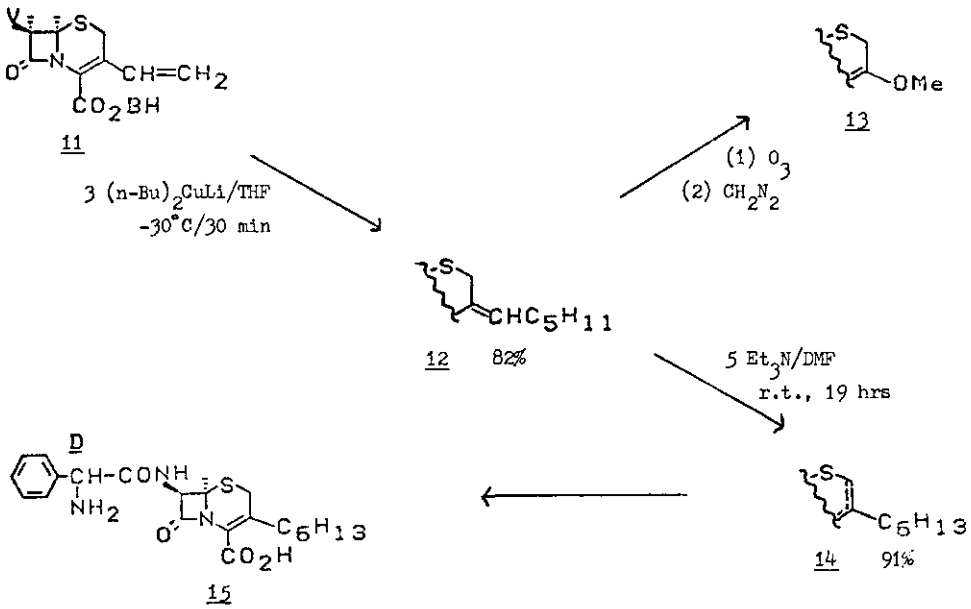


Compound 5 was then converted to the Δ^3-derivative by sulfur oxidation and reduction.[4,5] The side chain was then cleaved[6,7] and the D-α-phenylglycine derivative 7 was prepared.

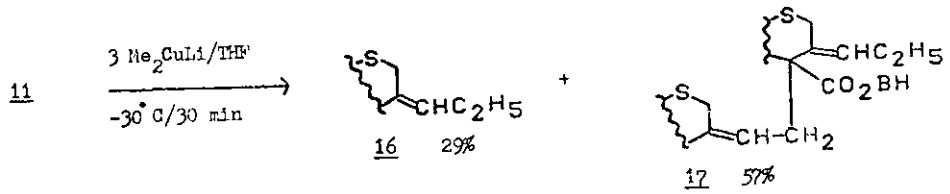
The Corey-Posner reaction[8] on the Δ^2-iodomethyl derivative 8 with lithium di-n-butylcuprate gave 17% C(3)-amyl 9 plus 30% C(3)-methyl 10, i.e. the reduced product. This sequence has been studied by workers at Glaxo.[9]



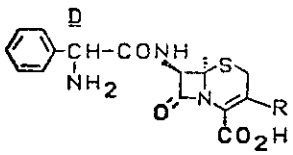
Another route to C(3)-lipophilic cephems, however, is via 1,6-conjugate addition of lithium di-n-butylcuprate with the C(3)-vinyl cephem[10] 11 which occurred in 82% yield to give the exocyclic olefin 12[11]. Proof of structure was by physical data (nmr, ir, mass spec.) and by the conversion to the C(3)-methoxy derivative 13.



Use of less reactive organocuprates, for example lithium dimethylcuprate, resulted in lower yields (29%) of the exomethylene derivative 16[12]. The major product was 17 (57%), presumably resulting from the Michael addition of the intermediate cuprate onto the starting material. The reaction of cuprate intermediates with electrophiles is well known.[13]



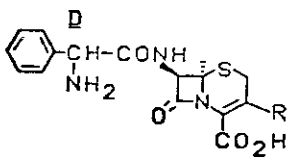
The exocyclic double bond in 12 proved somewhat resistant to isomerization, requiring 5 equivalents of triethylamine in N,N-dimethylformamide at room temperature for 19 h. to give a 96% yield of a mixture of the olefins 14 after chromatography. Sulfur oxidation (162-163°C), reduction[14] and side chain cleavage followed by acylation and deblocking gave the D-α-phenylglycine derivative 18[15].



	R
7	n-C_4H_9
18	n-C_6H_{13}

Table I shows the in-vitro microbiological activity of the various C(3)-alkyl-substituted cephems with the D-α-phenylglycine side chain. Increasing the lipophilic character at C(3) appears to enhance the gram positive activity with concomitant loss in the gram negative antibacterial activity.

TABLE I



MIC (μg/ml)

R	Staph. aureus		Staph. epidermidis	H. influenzae (amp)	E. coli
	V41	S13E	222	CL	TEM
CH_3	8	64	8	16	8
Et	16	16	2	8	16
n-C_4H_9	4	4	0.5	8	32
n-C_6H_{13}	0.5	2	0.25	4	128

ACKNOWLEDGEMENT

The authors wish to thank J. L. Ott for the microbiological data, L. C. Blaszczak and H. A. Kirst for helpful discussions concerning organocuprate chemistry, and L. Huckstep, D. M. Berry, L. E. Sachs and D. C. Duckworth for HPLC data.

REFERENCES AND NOTES

1. D.O. Spry, Tetrahedron, 1983, 39, 2527.
2. H.O. House, Acc. Chem. Res., 1976, 9, 59.
3. L.C. Blaszczak, J. Winkler, and S. O'Kuhn, Tetrahedron Lett., 1976, 4405.
4. G.V. Kaiser, R.D.G. Cooper, R.E. Koehler, C.F. Murphy, J.A. Webber, I.G. Wright, and E.M. Van Heyningen, J. Org. Chem., 1970, 35, 2430.
5. Δ^3-isomer of 5: m/e 556; ir ($CHCl_3$) 1775 cm^{-1}; nmr ($CDCl_3$) δ 0.80 (m, 3, Me), 1.24 (m, 4, CH_2), 2.32 (m, 2, 3'-CH_2), 3.20, 3.40 (AB, J=16 Hz, 2, C(2) protons), 4.52 (s, 2, $PhOCH_2$), 4.96 (d, J=4 Hz, 1, H_6), 5.76 (d, d, J=4, 9 Hz, 1, H_7).
6. B. Fechtig, H. Peter, H. Bickel, and E. Vischer, Helv. Chim. Acta, 1968, 51, 1108.
7. nmr ($CDCl_3$) δ 0.80 (m, 3, Me), 1.24 (m, 4, CH_2), 1.72 (s, 2, NH_2), 2.32 (m, 2, 3'-CH_2), 3.20, 3.40 (AB, J=16 Hz, 2, C(2) protons), 4.60 (d, J=5 Hz, 1, H_6), 4.85 (d, J=5 Hz, 1, H_7).
8. E.J. Corey and G.H. Posner, J. Am. Chem. Soc., 1967, 89, 3911; E.J. Corey and G.H. Posner, J. Am. Chem. Soc., 1968, 90, 5615.
9. B. Laudon, B.R. Cowley, and S.B. Laing, Brit. Patent 144244, 28 July, 1976.
10. Fujisawa; T. Takaya, H. Taksugi, T. Masugi, H. Yamanaka, and K. Kawabata, U.S. Patent 4,423,213, 27 Dec., 1983.
11. 12: m/e 584; ir ($CHCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (m, 3, Me), 1.28 (m, 6, CH_2), 2.0 (m, 2, 3'-CH_2), 3.30 (m, 2, C(2) protons), 4.40 (s, 2, $PhOCH_2$), 5.09 (s, 1, H_4), 5.40 (d, J=4 Hz, 1, H_6), 5.66 (d, d, J=4, 10 Hz, 1, H_7), 5.72 (m, 1, olefinic H).
12. 16: m/e 542; ir ($CHCl_3$) 1768 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, J=7.8 Hz, 3, Me), 2.08 (m, 2, CH_2), 3.24, 3.36 (AB, J=12 Hz, 2, C(2) protons), 4.48 (s, 1, Ph OCH_2), 5.54 (d, J=4 Hz, 1, H_6), 5.68 (d, d, J=4, 10 Hz, 1, H_7), 5.72 (m, 1, olefinic H).
13. (a) E.S. Binkey and C.H. Heathcock, J. Org. Chem., 1975, 40, 2156; (b) R.G. Salomon and M.F. Salomon, J. Org. Chem., 1975, 40, 1488; (c) K.K. Heng and R.A.J. Smith, Tetrahedron, 1979, 35 425.
14. Δ^3-isomer of 14: m/e 600; ir ($CHCl_3$) 1768 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (m, 3, Me), 1.18 (m, 8, CH_2), 2.33 (m, 2, 3'-CH_2), 3.25 (AB, 2, C(2) protons), 4.53 (s, 2, $PhOCH_2$), 4.97 (d, J=5 Hz, 2, H_6), 5.73 (d, d, J=5, 9 Hz, H_7).
15. 18: nmr (D_2O, DCl) δ 0.90 (m, 3, CH_3), 1.33 (bs, 8, $(CH_2)_4$), 2.53 (bs, 2, C(3)-CH_2), 3.26 (s, 2, C(2) protons), 5.02-5.12 (DOH), 5.40 (s, 1, C(7) side chain methine), 5.72 d, J=4 Hz, 1, H_7), 7.52 (m, 5, Ph).

Received, 11th April, 1985