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Synthesis of a Highly Reactive 1,1-Dicyanomethylene-1-dethiacephalosporin

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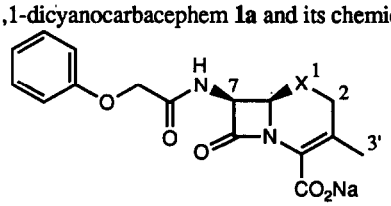
Abstract: Synthesis of the 1,1-dicyanomethylene-1-dethiacephalosporin **1a** is described. Substitution of the dicyanomethylene moiety for sulfur at position 1 of the cephem nucleus resulted in a highly reactive β-lactam antibacterial.

Since isolation of the first cephalosporin about forty years ago, countless analogs of these important antibacterials have been prepared, with the most common variations being at the C-7 acylamino side chain and the C-3' position. Additional changes have also been made to the dehydrothiazine ring itself, particularly at positions 1 and 2.[3]

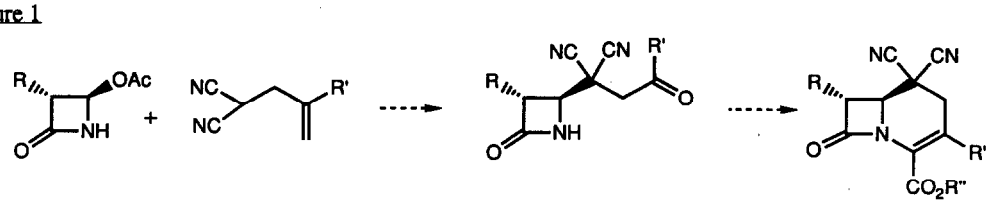
Carbon has been successfully substituted for sulfur at position 1, resulting in carbacephems which possess antibacterial activity similar to that of the corresponding cephalosporins and greater chemical stability.[4] We postulated that reactivity of the β-lactam carbonyl and antibacterial activity might be enhanced by increasing the electronegativity of the C-1 carbon, rendering it more "sulfur-like". The dicyanomethylene moiety has been suggested to be bioisosteric with oxygen,[5,6] and oxygen has been successfully substituted for the sulfur in cephalosporins, therefore we decided to test our hypothesis by preparing a 1,1-dicyanocarbacephem. We report here a synthesis of the 1,1-dicyanocarbacephem **1a** and its chemical reactivity.



1a: X = $C(CN)_2$
1b: X = S
1c: X = CH_2

Most of the reported syntheses of carbacephems are centered around a ketene-imine cycloaddition to construct the β-lactam ring, followed by a Wittig-type ring closure to form the 6-membered ring.[4a-d] Although cycloadditions of this type generally proceed to give the requisite *cis*-substituted β-lactam, for the 1,1-dicyanomethylene analog this route would require a potentially troublesome α,α-dicyano aldehyde. An alternative route would be addition of a malononitrile-type anion to a 4-acetoxy-azetidinone, followed by a Wittig-type closure of the six-membered ring (Figure 1). Epimerization at C-7 would afford the β-stereochemistry which is required for antibacterial activity.

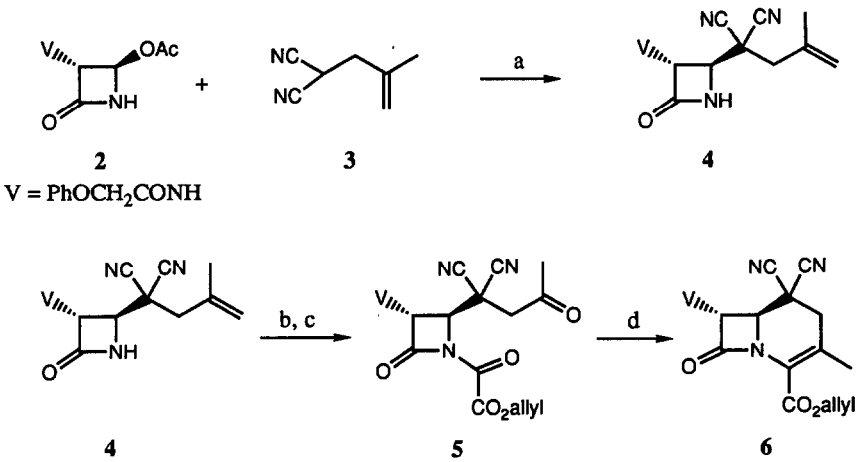
Figure 1



In addition to the accessibility of substituted malononitrile anions, an advantage to this route is the availability of enantiomerically pure azetidinones from the degradation of penicillin.

Synthesis of the 1,1-dicyanocarbacephem **1a** began as outlined in Scheme 1. Displacement of the known 4-acetoxyazetidinone **2**[7] with the malononitrile derivative **3**[8] proceeded stereospecifically to give C-4β-substituted azetidinone **4**. A conventional Wittig route using a triphenylphosphine ylide derived from **4** provided the desired product, however this route was time-consuming and suffered from poor reproducibility and dismal overall yield.[9] We then turned to the route described below in which oxalamide **5** served as the key intermediate. Ozonolysis of the olefin of **4**, followed by regioselective acylation of the β-lactam afforded **5**. The oxalamide was heated at reflux in xylene with triethylphosphite for a short period of time to provide the desired product **6**. Although this cyclization was inefficient, the overall yield was a considerable improvement over the conventional Wittig route, and the procedure was much less time-consuming. Triethylphosphite-induced ring closure has been widely used for the synthesis of penems, but to our knowledge, its use in cephem syntheses is rare.[10] We believe that the low yield in this step is due to the relative instability of the C-7 acylamino-substituted products such as **6**, since cyclization to afford a C-7 alkyl-substituted product proceeded in more acceptable yield.[11]

Scheme 1

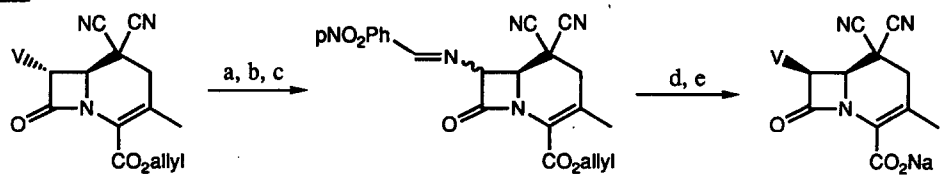


2 V = $PhOCH_2CONH$ **3** **4** **5** **6**

Conditions: (a) LHMDS, THF, -35°, 40 min (70%); (b) O_3, CH_2Cl_2, -45°, then DMS (75%); (c) $ClCOCO_2allyl$, iPr_2NEt, CH_2Cl_2, -78°, 30 min (100%); (d) $P(OEt)_3$, xylene, reflux, 20 min (30%)

While the C-7α stereochemistry was required to direct addition of **3** to **2**, a C-7β acylamino substituent is required for antibacterial activity. As shown in Scheme 2, inversion of the stereochemistry at C-7 was carried out *via* a known sequence to afford a separable mixture of α- and ß-imines **7** in a 1:1 ratio.[12] For cephalosporins, this inversion provides a 2:1 mixture of β/α imines, however in the case of the 1,1-dicyanocarbacephems, increased steric congestion on the β-face of the molecule results in the less favorable 1:1 ratio. In the case of other 1-substituted cephems, the C-7β epimer has been impossible to prepare.[13] Finally, treatment of β-**7** with phenoxyacetyl chloride afforded the amide at C-7 [14], and deprotection of the allyl ester provided the final product **1a**.[15]

Scheme 2



6 **7** **1a**

Conditions: (a) PCl_5, pyridine, isobutanol, CH_2Cl_2, 0°, 4h; (b) p-NO_2-benzaldehyde, $CHCl_3$, 15h (65% for steps a-b); (c) PhLi, THF, -78°, 15min (30% β-7 + 30% α-7); (d) PhOCOCl, CH_2Cl_2, 17h (76%); (e) $Pd(PPh_3)$, PPh_3, sodium 2-ethylhexanoate, 1:1 EtOAc, CH_2Cl_2, 0°, 40min (32%)

An indication of reactivity of the β-lactam was obtained by measuring the half-life (pH 7.4 phosphate buffer, 37° C) of **1a**. The 1,1-dicyanocarbacephem **1a** was much more reactive than its cephalosporin counterpart **1b**, with a half-life of 3.5h for **1a** as compared to >120h for the corresponding cephalosporin. The carbacephem **1c** has been reported to possess a half-life fifty times longer than the cephalosporin under more basic conditions.[4e] Another indication of β-lactam reactivity is the IR frequency of the β-lactam carbonyl,[16] and the frequencies for the 1,1-dicyanocarbacephem **1a**, the cephalosporin **1b**, and the carbacephem **1c** were 1770, 1758 and 1742 cm^{-1}, respectively.[4e] The increased absorption frequency of **1a**, along with its decreased stability lend validity to the proposal that increasing electronegativity of the C-1 carbon in a carbacephem increases β-lactam reactivity. More importantly, **1a** is a much more potent inhibitor of PBP's (Penicillin Binding Proteins) than the cephalosporin **1b**, with an IC_{50} of < 0.1 μM for **1a** vs >100 μM for **1b** against PBP 3 of *E. coli* UB1005. In conclusion, substitution of the dicyanomethylene moiety for sulfur at position 1 of a cephalosporin resulted in a ß-lactam antibacterial which was much more reactive than either its carbacephem or cephalosporin counterpart. Full details of the Penicillin Binding Protein and *in vitro* antibacterial activity for this class of compounds will be reported elsewhere.

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Spectral data for selected compounds:

Compound **4:** mp 189-191°; $[\alpha]_D^{20}$ = + 70.8° (c 1.0, MeOH); IR (KBr) 1776, 1659 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.63, 2.86 (ABq, 2H, J=14.1), 4.25 (d, 1H, J=2.6), 4.55 (s, 2H), 4.91 (dd, 1H, J=2.4, 6.7), 5.12 (s, 1H), 5.20 (s, 1H), 6.39 (br s, 1H), 6.89-7.38 (m, 6H); MS, *m/z* 338(M^+). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.24; H, 5.24; N, 16.50.

Compound **5:** IR ($CHCl_3$) 1840, 1755, 1730 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.46, 3.57 (ABq, 2H, J=20.0), 4.49, 4.58 (ABq, 2H, J=15.4), 4.83 (br d, 2H), 5.0 (m, 1H), 5.23-5.46 (m, 3H), 5.82-6.04 (m, 1H), 6.81-7.06 (m, 3H), 7.25-7.35 (m, 2H), 7.69 (d, 1H, J=7.2).

Compound **6:** $[\alpha]_D^{20}$= + 58.9° (c 0.23, $CHCl_3$); mp 185-192° (dec); IR ($CHCl_3$) 2255 (w), 1782, 1725, 1718, 1692 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.95, 3.07 (ABq, 2H, J=18.7), 4.13 (d, 1H, J=2.2), 4.57 (s, 2H), 4.80 (br d, 2H), 5.05 (dd, 1H, J=6.6, 2.2), 5.27-5.46 (m, 2H), 5.92-6.01 (m, 1H), 6.92 (d, 2H, J=8.8), 7.15 (t, 1H, J=6.4), 7.30-7.43 (m, 3H); MS; *m/z* 421 (M+H). Anal. Calcd. for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.80; N, 13.33. Found: C, 62.66; H, 4.87; N, 13.06.

Compound 7: ^{1}H NMR (400MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.04, 3.16 (ABq, 2H, J=17.8), 4.24 (d, 1H, J=5.2), 4.68-4.89 (m, 2H), 5.18-5.51 (m, 3H), 5.88-6.09 (m, 1H), 8.01 (d, 2H, J=8.6), 8.31 (d, 2H, J=8.6), 8.72 (d, 1H, J=1.6).

Compound 1a: IR(KBr) 3410, 2245(w), 1770,1690, 1602 cm^{-1}; ^{1}H NMR (400MHz, D_2O) δ 1.88 (s, 3H), 3.15 (s, 2H), 4.46 (d, 1H, J=4.4), 4.69 (s, 2H), 4.85 (s, 2H), 5.64 (d, 1H, J=4.4), 7.04 (d, 2H, J=8.0), 7.09 (t, 1H, J=7.6), 7.40 (t, 2H, J=7.6); MS *m/z* 403 (M+H), HRMS(FAB) calcd for $C_{19}H_{16}N_4O_5Na$ 403.1018, found 403.1020.

References and Notes:

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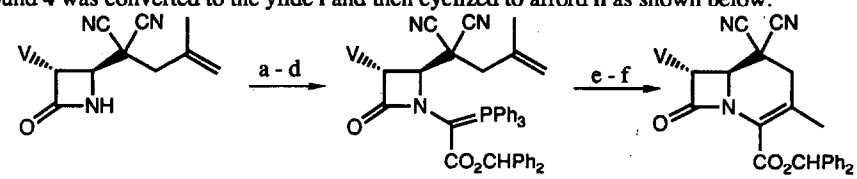
7. Compound **2** was prepared from 6-*epi*-penicillin V benzyl ester (ref. 7a) by the method of Stoodley (ref 7b): a) Claes, P., Vlietinck, A., Roets, E. and Vanderhaeghe, H. *J. C. S. Perkin I*, **1973**, 932. b) Stoodley, R. J. and Whitehouse, N. R. *J. C. S. Perkin I*, **1973**, 32.
8. Compound **3** was prepared by alkylation of methallyl chloride with the anion of malononitrile.
9. Compound **4** was converted to the ylide **i** and then cyclized to afford **ii** as shown below:



4 **i** **ii**

Conditions: (a) $CHOCO_2H$, DMF, 60h; (b) N_2CPh_2, EtOAc, 3h; (c) $SOCl_2$, 2,6-lutidine, THF, -25°, 1.5h (63% for a-c); (d) PPh_3, 2,6-lutidine, toluene, 85°, 15h (27%); (e) O_3, TFA, CH_2Cl_2, -25°, then DMS; (f) dioxane, reflux, 15h (49%for e-f)

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