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S(1)-C(2)-SECOCEPHEMS—II

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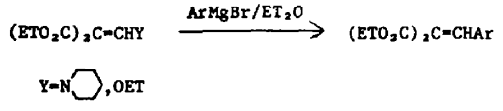
Abstract—Grignard reagents react with C(3)-electron rich (Cl, OMe, Sϕ, and morpholinyl) cephems to give *S*(1)-C(2)-seco products with the organic radical bonded to sulfur. A single-electron transfer mechanism is suggested to account for these results.

We recently reported the synthesis of *S*(1)-C(2)-secocephems via a Grignard reaction on *cis*-α-vinylhalocephem sulfoxides.[1]

We now wish to report another route to *S*(1)-C(2)-secocephems via an unusual reaction of Grignard reagents with cephalosporins containing electron rich heteroatoms at C(3), such as in Cl, OMe, Sϕ and morpholinyl.

Aryl Grignard reagents are known to undergo conjugate addition with β-amino[2] or β-alkoxy[3]-α,β-unsaturated esters to give β-aryl-α,-β-unsaturated esters, thus substituting the aryl group for the heteroatom (Scheme 1).

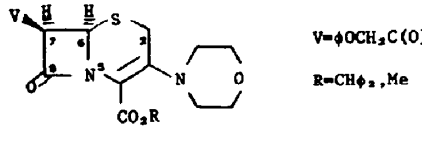


Scheme 1.

Having established from previous work[1,4,5] that under certain conditions the cephalosporin nucleus is stable to Grignard reagents (nucleus *p*-nitrobenzyl esters cannot be used), we chose the reaction of C(3)-substituted amino and C(3)-alkoxy cephems with Grignard reagents as a possible route to C(3)-alkyl and aryl[6,7] cephem derivatives.

RESULTS AND DISCUSSION

In order to determine the viability of the route, we chose initially to synthesize known C(3)-methyl cephem derivatives from the C(3)-morpholinyl cephem (**1**).



1

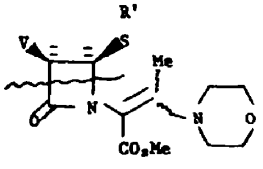
The C(3)-morpholinyl derivative (**1**) was prepared from the C(3)-chlorocephem[8,9] according to the work of Spitzer.[10] A THF soln of **1** was then treated with excess (3–5 equiv) MeMgBr at $-78°$ for 15–45 min. The reaction mixture quenched with either an equivalent amount of anhydrous HCl or aqueous NH_4Cl was extracted with ethyl acetate, the soln washed with water, brine, dried (Na_2SO_4), and chromatographed on silica gel using EtOAc/toluene to give the product. The corresponding C(3)-methyl cephem failed to react under these conditions. The product appeared to be a single spot on tlc and showed β-lactam absorption at 1755 cm^{-1}. The NMR spectrum of **2** (R = Me) showed the product to be an obvious mixture as evidenced by two sets of doublets for the β-lactam proton at 4.9, 5.1δ (J = 4 Hz), but only one doublet, doublet at 5.48δ (J = 4.8 Hz). The NMR spectrum also showed the presence of the morpholinyl group (3.2–3.8δ) and four different Me groups as singlets (R = Me; 1.97, 2.02, 2.19, 2.52δ) (R = CHϕ_2; 1.70, 1.80, 2.15, 2.40δ).

Acid catalyzed elimination of the morpholinyl group failed to give C(3)-methyl cephem, but rather yielded an enol, thus implying that the Grignard product still contained the enamine moiety. The UV spectrum (MeOH) of the Grignard product (R = Me) was 313 nm vs 333 nm for **1**, thus confirming the existence of the enamine. The NMR spectrum of the enol (R = Me) showed only one doublet at 5.1δ (J = 4 Hz) indicating a single product, but now showed two Me groups as singlets (R = Me; 2.0, 2.15δ) (R = CHϕ_2; 1.84, 2.17δ), one of which appeared to be a vinyl Me and the other we considered to be an S–Me.

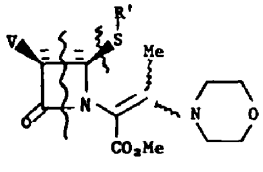
The reaction involving other Grignard reagents (EtMgBr, ϕMgBr) when followed by hydrolysis resulted in single products (72% with EtMgBr, 86% with ϕMgBr vs 67% for MeMgBr) whose NMR spectras showed only the vinyl Me as a singlet (2.15–2.23δ).

We infer from these results that there was *S*(1)–C(2)-bond cleavage with the C(2)-methylene becoming the vinyl Me and the organic radical being attached to S (Scheme 2).

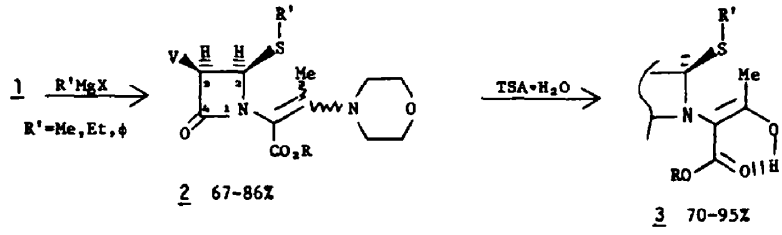
The mass spectrum data (electron impact) of the methyl esters further corroborates the assignments. Thus the mass spectrum of **2** (R = Me) shows the parent ion and the ion formed from it by loss of SR'. The predominate peak in all cases was at *m/e* 226,



m/e 226



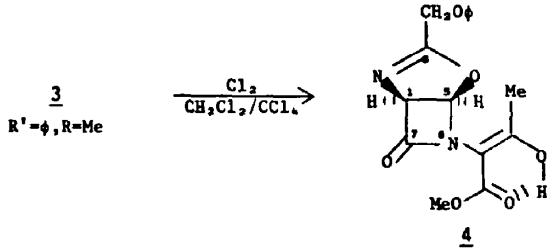
m/e 211



Scheme 2.

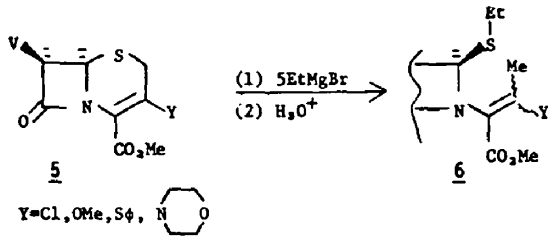
formed by horizontal cleavage of the β-lactam. In all cases we also see a small peak at m/e 211 which is formed by vertical cleavage plus loss of SR'. In general, the mass spectrum of the enol **3** (R' = Me, R = Me) showed the parent ion, the parent ion minus SR', and fragments from vertical cleavage and vertical cleavage plus loss of SR'.

The structure of the Grignard product was further corroborated by treating **3** (R' = ϕ, R = Me) with chlorine to give the enol oxazoline **4** (Scheme 3) whose structure was determined by mass spec and NMR ($CDCl_3$, β-lactam protons as doublets at 5.28, 5.97δ, J = 4 Hz).



Scheme 3.

C(3)-Methoxy derivatives[11] **5** (Y = OMe) also undergo the same transformation with Grignard reagents, but in somewhat lower yield (30%) to give **6** (Y = OMe) as a mixture of isomers (19% isomer A, 11% isomer B) (Scheme 4). The minor isomer B was identical to the product of **1** with ethyl Grignard followed by hydrolysis and O-methylation with diazomethane.



Scheme 4.

The C(3)–S-phenyl compound[12] **5**, (Y = Sϕ), under the same conditions, gave **6** (Y = Sϕ) in 62% yield, also as a mixture, while the C(3)-chloro compound **5**, (Y = Cl) gave **6** in 50% yield with Y being Et, which is formed from the intermediate vinyl chloride by excess Grignard. The structures of **6**, (Y = OMe, Et, Sϕ) are supported by mass and NMR spectral data.

The S(1)–C(2)-cleavage reaction with Grignard reagents goes well with cephalosporins with other side chains (thiopheneacetamido), but the reaction failed on the two sulfoxides (C(3)–Cl, OMe) that were tried.

MECHANISM

We considered two possible mechanisms for the Grignard reaction.

Two-electron transfer. This would involve the use of the Grignard reagent as a Lewis acid[13] to form **7**, thereby weakening the S(1)–C(2) bond followed by the attack of R'- at sulfur. However, the attack of a nucleophile at the center of high electron density is somewhat unlikely (Scheme 5).

One-electron transfer. The second mechanism, which is the one we prefer, involves a single-electron transfer pathway. One-electron transfer in Grignard reactions is well known through the work of Ashby.[14–16] Thus **5** would react with Grignard reagents to give **10**, which would undergo homolytic cleavage of the S(1)–C(2) bond to give **11**, followed by attack of the Grignard radical and hydrolysis to give the product **9**, (Scheme 6).

We are currently attempting to measure the reduction potentials of **5** (Y = Cl, OMe, Sϕ, morpholinyl) in order to determine the relationship between the Grignard reaction and the ability of the compounds to accept electrons.

EXPERIMENTAL

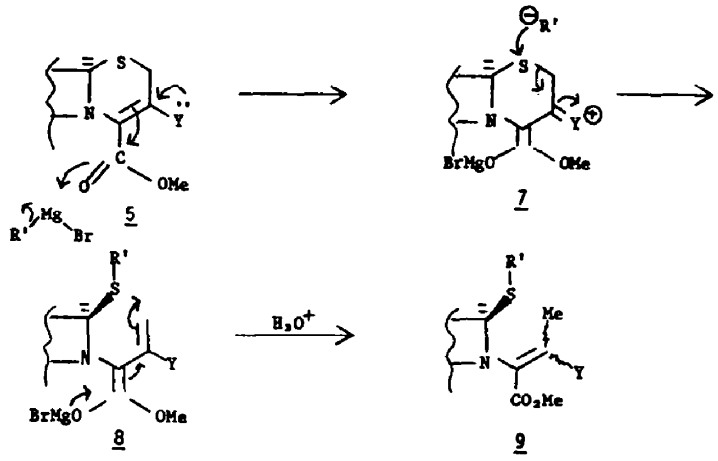
General. NMR spectra were run on a T-60 Varian, IR spectra were taken with a Perkin–Elmer 281 while the UV spectra were determined with a Cary 118. The mass spectral EI data were obtained on a CEC-21-110A.

(2R - cis) - 2 - (*Methylthio*) - α - [1 - (4 - *morpholinyl*)-*ethylidene*] - 4 - *oxo* - 3[(*phenoxyacetyl*)*amino*] - 1 - *azetidine-acetic acid, methyl ester*

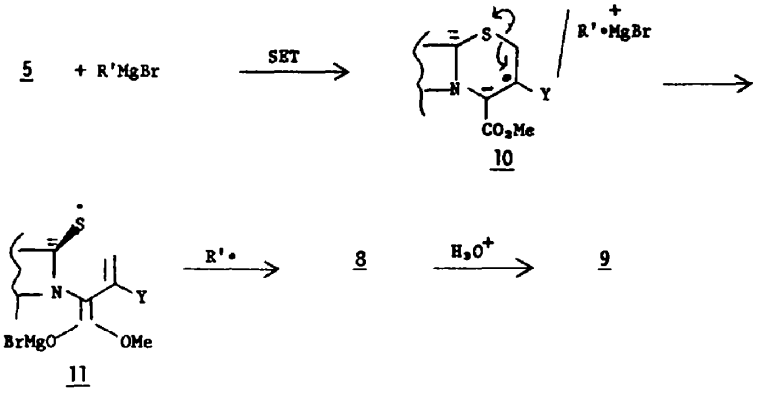
A cooled (−78°), stirred soln of **1**, (R = Me; 1.0 mm) in 45 ml THF was treated under Ar with 5 equiv of MeMgBr for 40 min (−78°). After which 5.0 equivs of anhyd HCl was added, or alternatively excess NH_4Cl aq, followed by warming to 0°. EtOAc was added and the extract washed with water, brine, dried over Na_2SO_4, evaporated and chromatographed on Merck silica gel using a toluene-EtOAc gradient to give 302 mg (67%) product as a white froth. IR ($CHCl_3$): 1755 cm^{-1}; MS m/e: 449, 402, 258, 226, 167, 139; ^1H NMR δ ($CDCl_3$): 1.97 (s, SMe), 2.02 (s, SMe), 2.19 (s, vinyl Me), 2.52 (s, vinyl Me), 3.2–3.8 (m, morpholinyl), 3.7 (s, CO_2Me), 4.6 (s, ϕOCH_2), 4.92 (d, J = 4 Hz, H2), 5.12 (d, J = 4 Hz, H2), 5.48 (d, d, J = 4, Hz, H3); UV (MeOH) ϵ_{313} = 20,248.

(2R - cis) - 2 - (*Ethylthio*) - α - [1 - (4 - *morpholinyl*)*ethylidene*] - 4 - *oxo* - 3[(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methyl ester*

Ethyl Grignard (5 equiv) using the experimental method above on 1 mm of substrate gave after chromatography 337 mg (73%) product as a white froth. IR ($CHCl_3$): 1755 cm^{-1}; MS m/e: 463, 402, 374, 288, 266, 167, 139; ^1H NMR δ ($CDCl_3$): 1.17 (t, Et), 2.17, 2.42 (both s, vinyl Me),



Scheme 5.



Scheme 6.

2.1–2.6 (m, Et), 3.2–3.8 (m, morpholinyl), 3.7 (s, CO_2Me), 4.57 (s, ϕOCH_2), 4.97 (d, J = 4 Hz, H2), 5.13 (d, J = 4 Hz, H2), 5.47 (d, d, J = 4, 8 Hz, H3); UV (MeOH) $\epsilon_{315} = 22{,}178$.

(2R - cis) - 2 - *Phenylthiol*) - α - [1 - 4 - *morpholinyl*)-*ethylidene*] - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methylester*

The reaction was run as above except that when the ϕMgBr was added a gum formed. The acetone/CO_2 bath was then replaced with an ice/H_2O bath until dissolution occurred (*ca* 1 min). The reaction was then allowed to go for 30 min at −78°. Normal work-up followed by chromatography gave 441 mg product (86%) as a white froth from 1 mm substrate. IR ($CHCl_3$): 1755 cm^{-1}; MS *m/e*: 511, 433, 402, 226, 167, 139; ^1H NMR δ ($CDCl_3$): 2.23 (s, vinyl Me), 2.38 (s, vinyl Me), 3.2–3.8 (m, morphilinyl), 3.7 (CO_2CH_3), 4.57 (s, ϕOCH_2), 5.3–5.7 (m, H2, H3); UV (MeOH) $\epsilon_{317} = 22{,}243$.

(2*R* - *cis*) - 2 (*Ethylthio*) - α - (1 - *methylpropylidene*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methyl ester*

Reaction was run on 625 mg (1.63 mm) using 5.0 equivs EtMgBr in 50 ml THF at −78°/Ar/15 min. Excess 1N HCl was added and the reaction warmed to 0°. EtOAc was added and the extract washed with H_2O, brine, dried and chromatographed on Merck silica using toluene–EtOAc gradient to give 12% starting material, 10% delta-2-starting material and 323 mg (49%) product (62% corrected for starting material). IR ($CHCl_3$): 1760 cm^{-1}. MS *m/e*: 406, 377, 345, 317, 285, 237, 216, 176, ^1H NMR δ ($CDCl_3$): 1.03–1.30 (m, Ets), 2.2–2.6 (m, Ets), 3.78 (s, CO_2CH_3), 4.57 (m, ϕOCH_2), 5.1–5.2 (m, H2), 5.65 (d, d, J = 4, 8 Hz, H3).

(2R - cis) - 2 - (*Ethylthoi*) - α - (1 - *methoxyethylidene*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methyl ester*

Run as above to give:

Isomer A (19%). IR ($CHCl_3$): 1759 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.13 (t, Et), 2.2–2.6 (m, Et), 2.53 (s, vinyl Me), 3.73 (s, CO_2CH_3), 3.83 (s, OMe), 4.57 (s, ϕOCH_2), 5.13 (d, J = 4 Hz, H2), 5.59 (d, d, J = 4, 9 Hz, H3).

Isomer B (11%). IR ($CHCl_3$): 1755 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.17 (t, Et), 2.23–2.67 (m, Et), 2.25 (s, vinyl Me), 3.75 (s, CO_2CH_3), 3.90 (s, OMe), 4.60 (s, ϕOCH_2), 5.24 (d, J = 4 Hz, H2), 5.46 (d, d, J = 4, 8 Hz, H3).

(2R - cis) - 2 - (*Ethylthio*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)-*amino*] - α - [1 - (*phenylthio*)*ethylidene*] - 1 - *azetidine-acetic acid, methyl ester*

IR ($CHCl_3$): 1765 cm^{-1}; MS *m/e*: 425, 377, 315, 283, 249, 237. MS (FD): 486; ^1H NMR δ ($CDCl_3$): 1.00–1.33 (m, Et), 2.0–2.6 (m, Et), 2.22 (s, vinyl Me), 3.75 (s, CO_2CH_3), 6.23 (s, ϕOCH_2), 5.3–5.8 (m, H2 + H3).

[(2R - cis), (E)] - α - (1 - *Hydroxyethylidene*) - 2 - (*methylthio*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methyl ester*

219 mg (0.48 mm) of the morpholinyl derivative in 10 ml THF was treated with 1.25 equiv of TSA·H_2O at room temp for 1 hr. EtOAc was added and the extract washed with H_2O, $NaHCO_3$, brine, dried and evaporated to 126 mg

(68%) product. IR ($CHCl_3$): 1760 cm^{-1}; MS *m/e*: 380, 365, 333, 288, 223, 190, 176, 142; ^1H NMR δ ($CDCl_3$): 2.00 (s, SMe), 2.16 (s, vinyl Me), 3.83 (s, CO_2CH_3), 4.58 (s, ϕOCH_2), 5.07 (d, J = 4 Hz, H2), 5.53 (d, d, J = 4, 10 Hz, H3), 12.3 (bs, vinyl OH); UV (methanol) ϵ_{267} = 19,021.

[(2R - cis), (E)] - α - (1 - *Hydroxyethylidene*) - 2 - (*ethylthio*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*aminol*] - 1 - *azetidineacetic acid, methyl ester*

IR ($CHCl_3$): 1760 cm^{-1}; MS *m/e*: 394, 365, 333, 318, 288, 237, 204, 176. ^1H NMR δ ($CDCl_3$): 1.17 (t, Et), 2.17 (s, vinyl Me), 2.47 (q, Et), 3.83 (s, CO_2CH_4), 4.58 (s, ϕOCH_2), 5.12 (d, J = 5 Hz, H2), 5.54 (d, d, J = 5, 8 Hz, H3), 12.4 (bs, vinyl OH); UV (methanol) ϵ_{267} = 18,094.

[(2R - cis), (E)] - α - (1 - *Hydroxyethylidene*) - 2 - (*phenylthio*) - 4 - *oxo* - 3 - [(*phenoxyacetyl*)*amino*] - 1 - *azetidineacetic acid, methyl ester*

IR ($CHCl_3$): 1763 cm^{-1}; MS *m/e*: 397, 370, 332, 302, 288, 256, 222; ^1H NMR δ ($CDCl_3$): 2.23 (s, vinyl Me), 3.67 (s, CO_2CH_3), 4.53 (s, ϕOCH_2), 5.33–5.67 (m, H2 + H3), 12.2 (bs, vinyl OH); UV (methanol) ϵ_{254} = 21,690 (broad peak).

[(5R - cis), (E)] - α - (1 - *hydroxyethylidene*) - 7 - *oxo* - 3 - (*phenoxymethyl*) - 4 - *oxa* - 2, 6 - *diazabicyclo*[3.2.0]*hept* - 2 - *ene* - 6 - *acetic acid, methyl ester*

A cooled (+5°), stirred soln of **3**, (R = Me, R′ = ϕ), (138 mg, 0.312 mm) in 20 ml 1:1 CH_2Cl_2/CCl_4 was treated with 3.0 equiv Cl_2 for 5 min and then allowed to stand at room temp for 5 min. The soln was evaporated to dryness and azeotroped several times using CH_2Cl_2. Chromatography on Merck silica using a toluene–EtOAc gradient gave 24 mg (23%) product. IR ($CHCl_3$): 1775 cm^{-1}; MS (FD) *m/e*: 332; ^1H NMR δ ($CDCl_3$): 1.92 (s. vinyl Me), 3.82 (s, CO_2CH_3), 4.80 (s, ϕOCH_2), 5.28 (d, J = 4 Hz, H1), 5.97 (d, J = 4 Hz, H5), 12.33 (s, vinyl OH).

(2R - cis) - 2 - (*Ethylthio* - α - [1 - (4 - *morpholinyl*)*ethylidene*] - 4 - *oxo* - 3 - [(2 - *thiopheneacetyl*)*amino*] - 1 - *azetidineacetic acid, benzyhydryl ester*

A cooled (−78°), stirred soln of the morpholine enamine benzhydryl ester of cephalothin (1.0 mm) in 25 ml THF was treated under Ar with 5.0 equiv EtMgBr for 30 min. Excess NH_4Cl aq was added and the mixture warmed to 0°. EtOAc was added and the extract washed with H_2O, brine, dried, (Na_2SO_4), evaporated and chromatographed on silica gel using a toluene–EtOAc gradient to give 454 mg (65.5%) product as a froth. IR ($CHCl_3$): 1755 cm^{-1}; MS *m/e*: 605, 394, 334, 276, 247, 227, 199, 167; ^1H NMR δ ($CDCl_3$): 0.80–1.18 (m, Et), 2.07 (s, vinyl Me), 2.0–2.4 (m, Et), 3.23–3.73 (m, morpholinyl), 3.78 (s, thiophene methylene), 4.80–4.97 (m, H2), 5.27 (d, d, J = 4, 8 Hz, H3).

[(2R - cis), (E) - α - (1 - *Hydroxyethylidene*) - 2 - (*ethylthiol*) - 4 - *exo* - 3 - [(2 - *thiopheneacetyl*)*amino*] - 1 - *azetidineacetic acid, benzyhydryl ester*

The enamine (454 mg, 0.749 mm) in 25 ml THF was treated with 1.25 equiv TSA·H_2O and allowed to react at r.t. 1 hr. EtOAc was added and the extract washed with H_2O, $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated to 0.364 g (90.5%) product as a yellow froth. IR ($CHCl_3$): 1765 cm^{-1}; MS *m/e*: 463, 430, 387, 326, 312, 297, 265, 247, 227, 206, 184, 167, 146, 97; ^1H NMR δ ($CDCl_3$): 1.0 (t, J = 7 Hz, Et), 2.07 (s, vinyl Me), 2.13–2.40 (m, Et), 3.77 (s, thiophene methylene), 5.0 (d, J = 4 Hz, H2), 5.37 (d, d, J = 4, 8 Hz, H3).

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