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Rearrangement and Degradation of Cephalosporins and Penicillins in the Presence of Mercury(II) Trifluoroacetate

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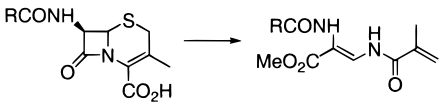
ABSTRACT

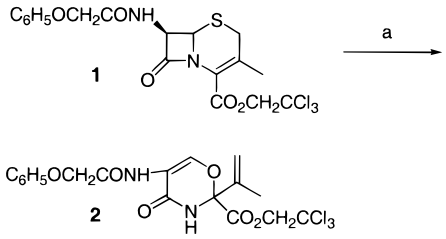


Cephalosporins and penicillins rearrange under the influence of mercury(II) trifluoroacetate in methanol to non-β-lactam products. The mechanisms of the rearrangements are different in the two cases. Whereas the open-chain aminoacrylic acid derivative 4 is produced from cephalosporins, the oxazole 7 and the propionamide 6 derivatives are the products from penicillins.

Differently substituted cephalosporins are of continued interest in targeting novel β-lactam derivatives with different β-lactamase or human leukocyte elastase enzyme inhibitory properties. The aim of our investigations is to find new substitution types and patterns for the dihydrothiazin ring of cephalosporin sulfides and sulfones. According to our current investigations[1] the 2-CH_2 group of the cephalosporin sulfones is a good target for electrophilic reagents owing to the adjacent SO_2 group and double bond, whereas in the corresponding sulfides the nucleophilic character is more pronounced. Acyloxylation of olefins (Treibs reaction) and ketones by mercury(II) acetate is a well-known procedure.[2] Considerably fewer examples are known for the hydroxylation or amination of double bonds by mercury(II) trifluoroacetate.[3] In early penicillin chemistry mercury(II) acetate was used for opening of the thiazolidine ring and conversion of the penam ring to 4-acetoxy-azetidinones;[4−6] acetoxylation of the cephem Δ^2-double bond is also known.[7]

Several years ago we studied the reaction of deacetoxycephalosporin with mercury(II) trifluoroacetate in dichloromethane in an attempt to functionalize the allylic 3-Me group. The reaction resulted in the formation of new 2*H*-[1,3]-oxazin derivatives **2** (Scheme 1).[8] Since then only one example was found for the use of mercury(II) trifluoroacetate in the cephalosporin chemistry, namely, the exchange of the 4-*S*-R

Scheme 1



a. $Hg(OCOCF_3)_2$,CH_2Cl_2, r.t.

(1) Gunda, T. E.; Szöke, G. N. *Tetrahedron* **1998**, *54*, 6565−6570.
(2) For reviews, see: (a) Rawlinson, D. J.; Sosnowsky, G. *Synthesis* **1973**, 567−602. (b) Arzoumanian, H.; Metzger, J. *Synthesis* **1971**, 527−536
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(4) Stoodley, R. J.; Whitehorse, N. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 32−35
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(6) Branch, C. L.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2268−2275
(7) Slusarchyk, W. A.; Applegate, H. E.; Cimarusti, C. M.; Dolfini, J. E.; Funke, P.; Puar, M. *J. Am. Chem. Soc.* **1978**, *100*, 1886−1892
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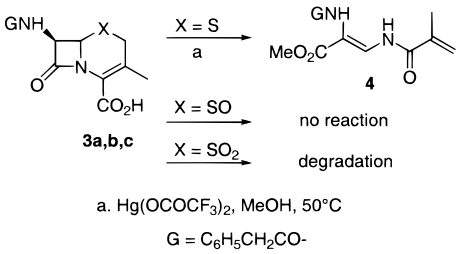
Scheme 2



group of an azetidinone with an intramolecular OH group under the influence of this Hg salt in an oxacephem synthesis.[9] Recently we reinvestigated this reaction, as we were curious to know whether mercury(II) trifluoroacetate would react with the sulfur (the preferred route in the case of sulfides), whether a possible solvomercuration would occur at C-2 when using the sulfones, or whether the Δ^3-double bond would be attacked.

When **3a** (X = S, Scheme 2) was allowed to stand in a methanol solution with Hg(II) trifluoroacetate, a sluggish reaction occurred, which was incomplete after 6 h at 50 °C and yielded an insoluble material, presumably undefined Hg salts. However, if the reaction mixture was heated for several hours with 4 equiv of the reagent, a well-defined compound was obtained in a moderate yield.[10] According to spectroscopic data, it lacks the β-lactam ring and the carboxyl group. Its mass spectrum exhibited a parent ion at *m*/*z* 302. The molecule was finally assigned the oxazoline structure **4** with the aid of X-ray diffraction (Figure 1). Under the same

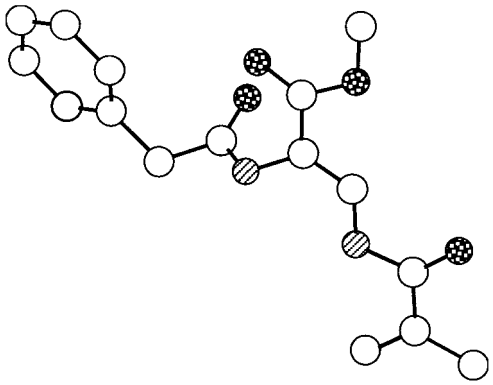
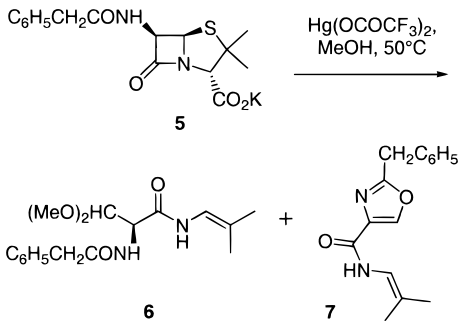


Figure 1. X-ray crystal structure of **4**.

reaction conditions the corresponding sulfoxide **3b** (X = SO) could be recovered unchanged, whereas extensive degradation was observed with the sulfone **3c** ($X = SO_2$).

To compare the behaviors of the cephem and penicillin ring systems, penicillin G was submitted to the same experiment. When the above procedure with Hg(II) trifluoroacetate in methanol solution was applied, two completely different products were obtained after chromatographic workup: **6** and the oxazole **7** (Scheme 3).[10] Stoodley and

Scheme 3



co-workers have published several very detailed investigations on the degradation of penicillanic acid derivatives to monocyclic azetidin-2-ones using mercury(II) acetate in acetic acid.[4,11–13] Although our products are not exactly the

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(10) **Salient Experimental Details.** A solution of 1.8 g of **3a** (X = S) in 100 mL of dry methanol was added to dried Hg(II) trifluoroacetate, prepared previously from 3.6 g of red HgO and trifluoroacetic acid. The mixture was stirred for 6 h at 50 °C, and after the mixture cooled, H_2S was bubbled through it for about 30 min. It was allowed to stay in the cool overnight. The precipitate was filtered off with the aid of Celite and washed with methanol. The methanol solution was concentrated and chromatographed on silica gel (toluene/EtOAc 3:1). **Methyl 3-(2-methyl-acroylamido)-2-phenylacetylamino-acrylate (4):** 0.86 g (58%), mp 115−116 °C (2-propanol/ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02 (d, 3 H, J = 1.3 Hz, CH_3), 3.71 (s, 2H, $PhCH_2$), 3.74 (s, 3 H, OCH_3), 5.56 (q, H, J = 1.3 Hz, $=CH_2$), 5.98 (s, H, $=CH_2$), 7.3−7.5 (m, 5H, aromatic), 7.72 (br s, H, side-chain CONH), 7.83 (dd, H, J_1 = 10.7 Hz, J_2 = 0.7 Hz, ring −CH<), 11.0 (d, H, J = 10.7 Hz, ring NH). ^{13}C NMR (200 MHz, $CDCl_3$): δ 18.3 (CH_3), 44.3 (CH_2Ph), 52.7 (OCH_3), 108.5 (C), 122.2 (CH), 122.5 (CH_2), 128.0 (CH), 129.3 (2 × CH arom.), 129.4 (2 × CH arom.), 133.6 (C), 138.7 (C), 165.1 (CO), 165.8 (CO), 170.1 (CO). MS (EI): *m*/*z* (%) 302 [M^+], 271 [M^+ − OMe], 211, 184, 167, 140, 91, 69 (100). $C_{16}H_{18}N_2O_4$ (302.331): calcd N 9.27; found N 9.48. X-ray diffraction: monoclinic $P2_1/n$, a = 16.744 Å, b = 4.719 Å, c = 19.995 Å, β = 102.7°, ρ_{calc} = 1.30 g/cm^3. Data were collected at 293 K on a Enraf Nonius MACH3 diffractometer, Mo Kα radiation. The structure was solved using the SIR-92 and SHELX-97 program suites, R(F)= 0.058 for 2539 reflections, 199 parameters. **3,3-Dimethoxy-*N*-(2-methyl-propenyl)-2-phenylacetylamino-propionamide (6)** and **2-benzyl-oxazole-4-carboxylic acid (2-methyl-propenyl)amide (7):** prepared from 3.6 g of penicillin G potassium salt (**5**) and 4.4 g of HgO, as above. **6**: 0.81 g (26%), mp 119−122 °C ($CHCl_3$/ether). IR (KBr): ν = 3299, 1635, 1534, 1079, 1124 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.56 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 3.37 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 3.62 (s, 2 H, CH_2Ph), 4.54 (dd, 1 H, CONH−C*H*<), 4.64 (d, 1 H, C*H*($OMe)_2$), 6.44 (d, 1 H, J = 10 Hz, vinylic H), 6.56 (broad d, 1 H, J = 6 Hz, CON*H*-CH<), 7.31 (m, 5 H, aromatic), 7.92 (broad d, 1 H, J = 10 Hz, CON*H*-CH=). MS (EI): *m*/*z* (%) 288 [M^+ − 32], 218, 191, 114, 91 (100). $C_{17}H_{24}N_2O_4$ (320.389): calcd C 63.75, H 7.55, N 8.74, S 0.0; found C 63.27, H 7.43, N 9.05, S 0.08. **7**: the oily rough product was rechromatographed (CCl_4/10% Et_2O), giving 0.38 g (15.3%) of an oil, which slowly crystallized on long standing, mp 52−60 °C (lit.[2] mp 72−74 °C). IR (KBr): ν 3399, 1674, 1597, 1510, 1094, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 4.11 (s, 2 H, CH_2Ph), 6.62 (d, 1 H, J = 9.8 Hz, vinylic H), 7.3 (m, 5 H, aromatic), 8.13 (s, 1 H, oxazole), 8.25 (broad d, 1 H, J = 9.8 Hz, NH). MS (EI): *m*/*z* (%) 256 [M^+], 186, 138, 91 (100). $C_{15}H_{16}N_2O_4$ (256.305): calcd C 70.29, H 6.29, N 10.93, S 0.0; found C 69.91, H 6.49, N 11.01, S 0.06.

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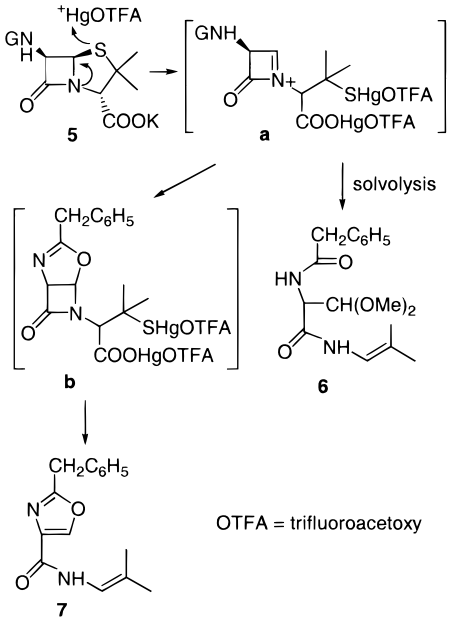
(12) Corbett, D. F.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans 1* **1974**, 185−187

(13) Stoodley, R. J.; Watson, N. S. *J. Chem. Soc., Perkin Trans 1* **1975**, 883−888

same as those described earlier, nevertheless they are obviously the result of a similar process.

The formations of **6** and **7** can be explained by analogy with literature findings.[4,11−13] As is depicted in Scheme 4,

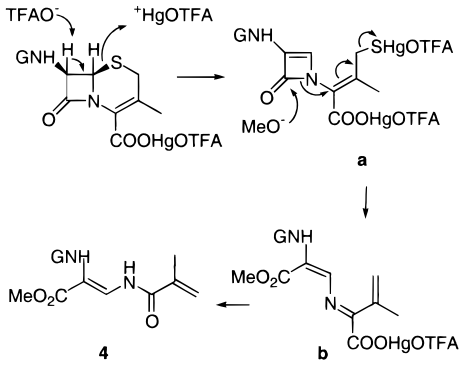
Scheme 4



the initial attack of the Hg^{2+} results in a 1−5 bond cleavage leading to the formation of the imminium intermediate **a**. This, in turn, solvolyzes to **6** or cyclizes to **b** and decomposes to **7**. The latter **b** → **7** type opening of the β-lactam ring is a known feature of this type of oxazolines (or the analogous thiazolines).

In the case of **3a** the presence of the 2*H*-thiazine ring directs the reaction in another way. It is reasonable to assume that the initial Hg → S attack leads to the 1−2 ring scission, with a parallel attack of base at C-6, and this intramolecular β-elimination results in **a** (Scheme 5). Simultaneous methanolysis of the β-lactam ring and elimination of the SHgOTFA moiety leads to **b**. It is difficult to explain precisely the last step resulting in the formation of **4**; the decarboxylation must be followed by further oxidative steps on the C═N bond. Presumably water adds to the imine bond of **b**, and the resulting aminoalkohol is oxidatively decarboxylated.

Scheme 5



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Supporting Information Available: Crystallographic coordinates of **4** are available in CIF file format. This material is available free of charge via the Internet at http://pubs.acs.org.

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