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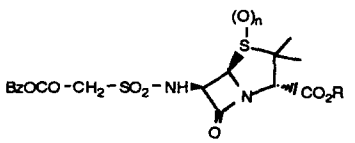
Solvolysis of the Methoxymethyl Protecting Group in Penicillin Derivatives.

Sophie Vanwetswinkel[a], Vincent Carlier[a], Jacqueline Marchand-Brynaert[b] and Jacques Fastrez[a]*.

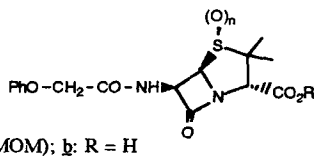
Lab. de Biochimie Physique et des Biopolymères [a], Lab. de Chimie Organique de Synthèse [b],
Université Catholique de Louvain, Place L. Pasteur, 1, Bte 1B, B1348, Louvain-la-Neuve, Belgium.

Abstract: The methoxymethyl (MOM) moiety, used as protecting group for the carboxyl function of penicillin derivatives, their sulfoxides and sulfones, could be easily cleaved in aqueous methanol at room temperature. The rate of deprotection by solvolysis is not sensitive to the nature of the substituent in position 6, but depends on the state of oxidation of the thiazolidine sulfur.

The syntheses of complex organic compounds require the use of orthogonal protecting groups [1]. As part of a program in which we prepared bifunctional activity labels including mechanism-based inhibitors derived from 6-aminopenicillanic acid [2], we selected the methoxymethyl moiety (MOM) [3] for masking the carboxyl function of the 6-sulfonylamidopenicillanic acid sulfone inhibitor **1b** [4]. Several standard deprotection conditions[1] were then tested for the cleavage of the MOM group from the penam sulfone **1a**, *i.e.* reaction with aqueous HCl (0.5N or 1N) in organic solvent [5,6] (dioxane, dioxane + anisol, dioxane + DMF), and reaction with $MgBr_2$ in organic solvent [7] (CH_2Cl_2, DMF). These deprotection conditions were always accompanied by some β-lactam degradation. It was then found that an efficient and selective MOM deprotection could take place under very mild neutral conditions in solvents of high ionising power. Overnight incubation at 21°C of the sulfone **1a** in a mixture of methanol and water (60% MeOH) gave quantitatively the deprotected product **1b**. The deprotection of the MOM group of the penicillin derivative **3a** appeared to be slower in the same conditions. To study the influence of the state of oxidation of the thiazolidine sulfur on the rate of solvolysis of the MOM esters, the sulfoxide **2a** and the penicillin V derivatives **4a**, **5a** and **6a** were prepared [8].



1 n = 2
2 n = 1 (β)
3 n = 0



4 n = 2
5 n = 1 (β)
6 n = 0

a: R = CH_2OCH_3 (MOM); b: R = H

Compound	k min^{-1}
1a	4.1 x 10^{-3}
2a	1.9 x 10^{-3}
3a	5.6 x 10^{-4}
4a	4.2 x 10^{-3}
5a	2.1 x 10^{-3}
6a	4.5 x 10^{-4}

The solvolytic deprotection of these compounds and of **1a** and **3a** was followed by NMR spectroscopy (Bruker AM-500, CD_3OD-D_2O (60/40) at 25°C). The rate constants, determined by curve fitting of the intensity of the CH_2-MOM signal *versus* time, are given in the table. No β-lactam ring opening was detected. The rate of solvolysis of the MOM ester group is not sensitive to the nature of the substituent in position 6 as seen in the comparison of 6-sulfonylamidopenicillins **1a**, **2a** and **3a** *versus* 6-acylamidopenicillins **4a**, **5a** and **6a**; it increases when the state of oxidation of the thiazolidine sulfur

increases: k_{SO}/k_S = 4.1 and k_{SO_2}/k_{SO} = 2.0. This is consistent with the fact that uncatalysed hydrolysis of alkoxymethyl esters takes place via alkyl-oxygen fission and is favoured by electron withdrawing substituents on the parent acid [18]. Our conditions of MOM esters deprotection are mild enough to be applicable to any acid or base sensitive compound and particularly they can be useful in the field of penicillin chemistry [19].

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8. The sulfoxide **2a** [9] was obtained from the sulfur precursor **3a** [4] by oxidation with $NaIO_4$ [10] (phosphate buffer pH 6.8, dioxane, 3h, 20°C), or with magnesium monoperoxyphthalate [11] (CH_2Cl_2, reflux, 15h). In both cases, NMR analysis [12,13] of the crude products showed that the sulfoxide had the ß-configuration; the alpha-isomer could not be detected. The ß-sulfoxide of penicillin V MOM ester **5a** [14] was prepared similarly from **6a** and $NaIO_4$. The penicillin sulfone **4a** [15] was prepared by treatment of **6a** [16] with $KMnO_4$ [17] (HOAc-H_2O (4:1), 1h, -10°C to 0°C).
9. **2a**: ^1H NMR(500 MHz, $CDCl_3$): δ: 1.2 (s, 3H), 1.68 (s, 3H), 3.46 (s, 3H), 4.16 (ABq, 2H, J = 15.5Hz), 4.59 (s, 1H), 4.95 (d, 1H, J = 4.77 Hz), 5.17 (ABq, 2H, J = 12.1 Hz), 5.20 (ABd, 1H, J = 5.9 Hz), 5.27 (dd, 1H, J = 4.77 Hz and 11.1 Hz), 5.37 (ABd, 1H, J = 5.9 Hz), 6.88 (d, 1H, J = 11.1 Hz), 7.36 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 18.47, 19.24, 57.71, 58.31, 60.56, 66.32, 68.18, 74.91, 76.46, 92.00, 128.52, 128.59, 128.67, 134.47, 163.35, 167.30, 172.54. MS (DCI) (CH_4-N_2O) m/z : 489 (M+1).
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14. **5a**: ^1H NMR (500 MHz, $CDCl_3$) δ : 1.27 (s, 3H), 1.77 (s, 3H), 3.53 (s, 3H), 4.55 (s, 2H), 4.71 (s, 1H), 5.06 (d, 1H, J = 4.6 Hz), 5.27 (ABd, 1H, J = 5.9 Hz), 5.44 (ABd, 1H, J = 5.9 Hz), 6.12 (dd, 1H, J = 4.6 Hz and 10.5 Hz), 6.93 (m, 2H), 7.01 (m, 1H), 7.30 (m, 2H), 8.26 (d, 1H, J = 10.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 18.44, 19.31, 55.44, 58.24, 66.26, 66.93, 75.14, 76.43, 91.92, 114.75, 122.06, 129.55, 167.42, 168.12, 172.99. MS (FAB-MNBA) m/z 411 ($C_{18}H_{22}O_7N_2S$ + 1).
15. **4a**: ^1H NMR (500 MHz, $CDCl_3$) δ : 1.45 (s, 3H), 1.64 (s, 3H), 3.52 (s, 3H), 4.55 (s, 1H), 4.56 (s, 2H), 4.82 (d, 1H, J = 4.6 Hz), 5.27 (ABd, 1H, J = 5.9 Hz), 5.43 (ABd, 1H, J = 5.9 Hz), 6.18 (dd, 1H, J = 4.6 Hz and 10.5 Hz), 6.92 (m, 2H), 7.02 (m, 1H), 7.29 (m, 2H), 8.16 (d, 1H, J = 10.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 17.71, 20.07, 56.16, 58.20, 63.77, 64.50, 65.58, 66.89, 92.23, 114.74, 122.19, 129.59, 156.74, 166.14, 168.19, 173.37. MS (FAB-MNBA) m/z 427 ($C_{18}H_{22}O_8N_2S$ + 1).
16. **6a** was prepared from penicillin V potassium salt treated with $ClCH_2OCH_3$ in DMF for 1 h at 0°C and 2 h at 20°C. ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.62 (s, 3H), 3.51 (s, 3H), 4.48 (s, 1H), 4.56 (sharp ABq, 2H, J = 15.1 Hz), 5.32 (sharp ABq, 2H, J = 5.9 Hz), 5.60 (d, 1H, J = 4.3 Hz), 5.75 (dd, 1H, J = 4.3 Hz and 9.1 Hz), 6.93 (m, 2H), 7.04 (m, 1H), 7.32 (m, 2H), 7.32 (d, 1H, J = 9.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ : 26.63, 31.73, 58.01, 58.10, 64.53, 67.07, 67.69, 70.34, 91.56, 114.67, 122.27, 129.69, 156.84, 167.06, 167.69, 172.88. MS (FAB-MNBA)m/z 395 ($C_{18}H_{22}O_6N_2S$ + 1).
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