An Efficient Synthesis of 2-(Halogenomethyl)penems

Maria Altamura* and Enzo Perrotta

A. Menarini Industrie Farmaceutiche Riunite S.r.l., Chemical Research Department, via dei Sette Santi 3, I-50131 Firenze, Italy

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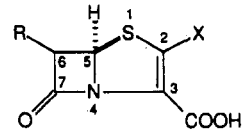
The penems 1 (Scheme I) are highly potent broad-spectrum β-lactam antibiotics structurally related to the naturally occurring penicillins, cephalosporins, and carbapenems.[1] While the substituent at C-6 is usually chosen to be 1(*R*)-hydroxyethyl (1), also characteristic of the naturally occurring carbapenem thienamycin,[2] or its close analog hydroxymethyl (2), a large differentiation is possible in the nature of the X substituent at C-2.[1b]

Following the interest in the synthesis of C-2-substituted penem derivatives, we have investigated a method for the functionalization of 2-substituted methyl derivatives (1, X = CH_2Y) which could allow the insertion of a variety of organic groups via reaction with the suitable nucleophilic reagent. The method should also take into account the extreme sensitivity of the penem nucleus to acidic and basic reagents and its low thermal stability.

Among the compounds of interest are the 2-(halogenomethyl)penems. A 2-(chloromethyl)penem (6, Scheme II) had been synthesized[3] from the corresponding alcohol 3 and an organic hydrochloride (pyridine hydrochloride, $MeONH_2$·HCl) under Mitsunobu conditions (DEAD, PPh_3). The procedure requires, however, the removal of the reagents by column chromatography. The method is therefore difficult to apply to a molecule of very limited stability under chromatographic conditions, such as the 2-(chloromethyl)penem. No report has been made on the synthesis and spectroscopic characterization of the even more unstable 2-(bromomethyl)- and 2-(iodomethyl)-penems. This method is, however, the only one reported for the preparation of 2-(chloromethyl)penems: as a matter of fact, when we applied to the penem series the procedure commonly used in the transformation of an allyl alcohol into the corresponding chloride,[4] namely the sequential use of methanesulfonyl chloride, 2,4,6-collidine, and lithium chloride in DMF, we obtained an incomplete reaction, the conversion of the alcohol 3 to the chloride 6 being less than 50%. The reaction yields were quite low, due to the need of a chromatographic separation in order to obtain sufficiently pure products.

We have also investigated the formation of the 2-(chloromethyl)penem 6 via the 2-[(diphenoxyphosphoryl)-methyl] derivative 4. A similar method has been recently applied to a carbapenem,[5] giving the 2-(chloromethyl) derivative as the sole product in fairly good yields.

Scheme I



(R)
1 R = CH_3–CH(OH)–
2 R = HO–CH_2–

Following this methodology we synthesized the 2-(phosphorylmethyl)penem 4 from the alcohol 3 by reaction with diphenyl phosphorochloridate in the presence of 4-(dimethylamino)pyridine at −50 °C. The phosphoryl derivative 4 was obtained in quite good yields (81%). The product is stable upon storage at 4 °C for several days. However, the subsequent treatment of 4 with either lithium chloride or trimethylsilyl chloride in methylene dichloride or DMF did not give, in any case, the 2-(chloromethyl) derivative 6: the starting material was recovered unchanged after 1 h under stirring at room temperature; longer reaction times or more drastic conditions led to complete decomposition of 4, giving a complex mixture of non-β-lactam products.

We finally achieved the clean and efficient preparation of 2-(chloro-, 2-(bromo-, and 2-(iodomethyl)penems 6–8 by treating the 2-(methylsulfonyl) derivative 5, easily prepared from the alcohol 3,[6] with the corresponding calcium halogenide in DMSO solution. After 3 h under stirring at room temperature we obtained the complete conversion of the mesylate 5 to the 2-(halogenomethyl)-penems 6–8. Transformation of the halogeno derivatives into various 2-methyl-substituted penems could be performed by simple reaction with the suitable nucleophilic reagent in the same DMSO solution in which the halogenides were formed. Alternatively, the halogenomethyl penems 6–8 could be easily isolated by diluting the DMSO solution with ethyl acetate and washing with iced water. Evaporation of the solvent gave the desired products in high purity grade (HPLC assay >95%). Yields were very high for the chloro and bromo derivatives (Cl: 90%, Br: 85% from the (hydroxymethyl)penem 3) and also quite good for the extremely unstable iodo derivative (75%). This is noteworthy for the latter two products, which have never been fully characterized.[7]

2-(Halogenomethyl)penems synthesized according to our method are dense oils which decompose in a few hours' time if stored at room temperature. The stability decreases going from the chloro to the iodo derivative. Nevertheless, it is possible to store the halogeno derivatives in chloroform solution at 4 °C: the chloro derivative did not show any appreciable decomposition after 3 days. The spectroscopic properties of the 2-(halogenomethyl)penems are summarized in Table I. Interestingly, we found an extreme dispersion in the ^{13}C chemical shift values for the three different compounds, from δ = +37.6 ppm for the 2-methylene of the chloro derivative to δ = −6.24 ppm for the iodide (δ = +58.1 ppm for 2-CH_2OH in 3 and δ = +63.8

(1) (a) Ernest, I. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 315–360. (b) McCombie, S. W.; Ganguly, A. K. *Med. Res. Rev.* **1988**, *8*, 393. (c) Perrone, E.; Franceschi, G. *Synthesis of Penems*. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin–Heidelberg, 1990; pp 613–704.

(2) Ratcliffe, R. W.; Albers-Schoenberg, G. Reference 1a; pp 227–314.

(3) Alpegiani, M.; Bedeschi, A.; Perrone, E. *Gazz. Chim. Ital.* **1985**, *115*, 393.

(4) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(5) Imuta, M.; Itani, H.; Ona, H.; Konoike, T.; Uyeo, S.; Kimura, Y.; Miwa, H.; Matsuura, S.; Yoshida, T. *Chem. Pharm. Bull.* **1991**, *39*, 672.

(6) Franceschi, G.; Perrone, E.; Alpegiani, M.; Bedeschi, A.; Battistini, C.; Zarini, F.; Della Bruna, C. *J. Antimicrob. Chemother.* **1989**, *23* (Suppl. C) 1 and references cited therein.

(7) To our knowledge, only spectroscopic (^1H NMR) evidence at low temperature was reported for a 2-(bromomethyl)penem but the product could not be isolated.[8] No report was available in the literature about 2-(iodomethyl)penems.

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Scheme II

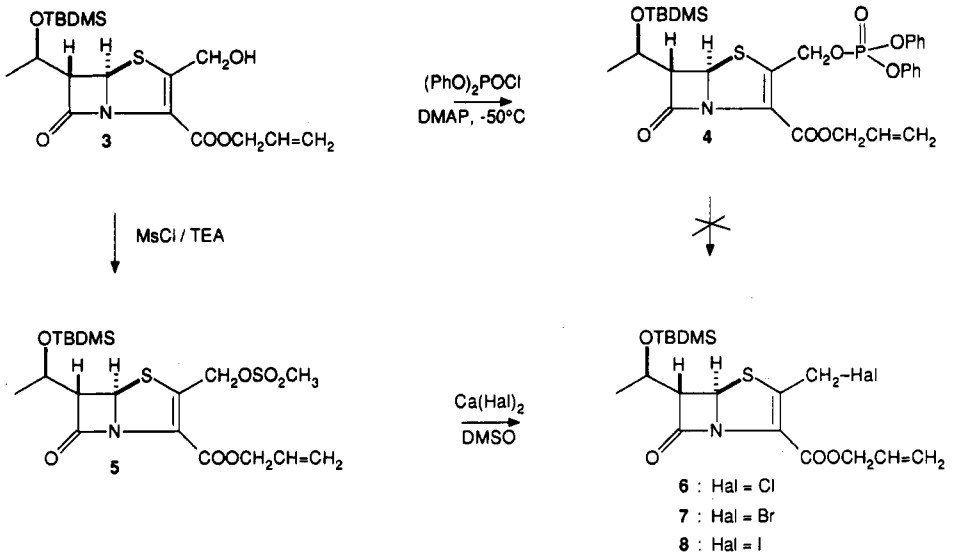


Table I. Spectral Data for 6–8

compound	^{1}H NMR:[a] $\delta_{CH_2\text{-Hal}}$ (J_{AB})	^{13}C NMR:[b] $\delta_{CH_2\text{-Hal}}$	UV: λ_{max} (nm)
6	4.62, 4.94 (J = 14 Hz)	37.6	248, 330
7	4.51, 4.81 (J = 12 Hz)	23.1	244, 336
8	4.50, 4.70 (J = 10 Hz)	−6.2	254, 348

[a] Spectra recorded at 200 MHz in $CDCl_3$. Chemical shift values for AB system are in ppm. [b] Spectra recorded at 50 MHz in $CDCl_3$. Chemical shift values are in ppm.

ppm for 2-CH_2OMs in **5**). This feature allowed us to follow the reaction also by ^{13}C NMR spectroscopy in d_6-DMSO.

The use of calcium halogenides in the synthesis of halogeno compounds from alcohols via the methylsulfonyl derivative has some precedent in the literature,[9] albeit limited in large part to the preparation of chloro- and bromoalkynyl compounds. To our knowledge, the method had not been applied to the synthesis of a complete series of halogeno derivatives of compounds with a complex molecular structure such as penems. In this case, the presence of several functional groups and the low stability of the β-lactam skeleton to temperature and pH changes limits the variety of possible experimental conditions. Furthermore, the method does not require anhydrous solvents nor reagents (the iodide can be synthesized from the commercially available $CaI_2 \cdot 4H_2O$).[10]

Our method does not seem to be applicable to the synthesis of 2-(fluoromethyl)penems. In fact, no reaction occurred by treating **5** with calcium fluoride in DMSO, probably due to the extremely low solubility of CaF_2.[11] On the other hand, the use of tetrabutylammonium fluoride as a soluble form of F^- [12] in a variety of solvents (dioxane, THF, DMSO) and at different reaction temperatures (from −78 °C to +20 °C) led to complex mixtures of non-fluorinated compounds.[13]

Some applications of the method to the synthesis of allylic and benzylic halogenides outside the β-lactam field are summarized in Table II. As shown in the table, the reaction could be easily applied to aliphatic and aromatic alcohols, giving the corresponding chloro, bromo, and iodo derivatives. In heterocyclic systems carrying a hydroxymethyl moiety (entries 2 and 3) the synthesis of halogeno derivatives could be achieved in moderate to good yields. No reaction occurred with a non-benzylic system such as 2-phenylethanol (entry 5), although the corresponding mesylate could be formed in good yield. When different kinds of hydroxy moieties were present on the same molecule (entries 3 and 6), the calcium halogenides reacted only with the allylic one, allowing the isolation of the halogeno derivative still carrying the mesylate group on the vinylic (entry 3) or phenolic (entry 6) hydroxy group.

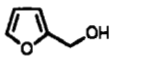
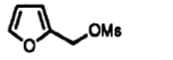
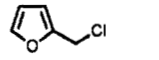
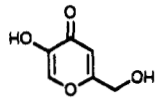
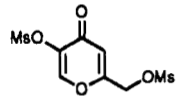
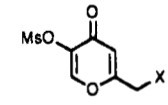
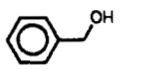
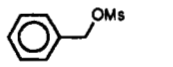
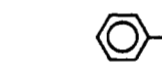
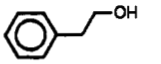
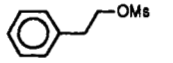
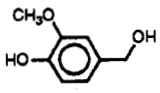
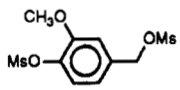
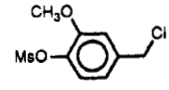
In our opinion, however, the major interest of the method lies in its application to the synthesis of labile or sensitive products, such as penems, allowing the simple and efficient synthesis of 2-(chloro-, 2-(bromo-, and 2-(iodomethyl)-penem derivatives from the corresponding alcohol. Reactivity and synthetic utility of the halogeno derivatives **6–8** are currently under investigation.

Experimental Section

NMR spectra were obtained using a Varian Gemini 200 spectrometer at 200 and 50 MHz for ^{1}H and ^{13}C spectra, respectively, with $CDCl_3$ as internal standard. HPLC and UV analyses were performed with a Perkin-Elmer Analyst liquid chromatograph equipped with a Perkin-Elmer 235 diode array detector and workstation. Chromatography was performed with a 5-μm C_{18} Hypersil 50 DS column (4.6 mm i.d. × 250 mm), eluting at a flow rate of 1.0 mL/min with a 20/80 mixture of water and acetonitrile (UV monitoring at 220 and 320 nm). Mass spectra were taken with a Hewlett-Packard 5988A spectrometer. In the EI spectra, samples were introduced via a direct inlet probe heated from 20°–250 °C at 45 °C/min. Ionization was achieved at an energy of 70 eV; ion source temperature was 200 °C. In the TS-MS spectra the mass spectrometer was fitted with a Hewlett-Packard thermospray ion source operated at 276 °C. The vaporizer temperature was 120 °C. Samples were dissolved in 0.1 M ammonium acetate in methanol and introduced by flow-injection into a Hewlett-Packard series 1050 liquid chromato-

(8) Perrone, E.; Franceschi, G. Reference 1c; p 685.
(9) (a) Jenkins, G. L.; Kellett, J. C., Jr. *J. Org. Chem.* **1962**, *27*, 624. (b) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1950**, 3650.
(10) Recently a report on the use of triphosgene for the synthesis of 2-(chloromethyl)cephems has been published (Goren, Z.; Heeg, M. J.; Mobashery, S. *J. Org. Chem.* **1991**, *56*, 7186). The method could in principle allow the preparation of 2-(chloromethyl)penems (no notice about the synthesis of bromo and iodo derivatives is made in the cited paper); it requires, however, anhydrous conditions and the use of a toxic and expensive reagent (triphosgene).
(11) See for example: Cotton, F. A., Wilkinson, G. *Advances Inorganic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 1987.
(12) Bohlmann, R. Synthesis of Halides. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 218 and references cited therein.
(13) No H–F coupling could be detected in the ^{1}H NMR spectrum.

Table II. Halogenides Prepared from the Corresponding Alcohols

entry	reagent	methylsulfonyl derivative (reaction time, yield)[a,c]	halogeno derivative (reaction time, yield)[b,c]	spectral data for halogeno derivatives: ^{1}H NMR[d] (δ)	spectral data for halogeno derivatives: ^{13}C NMR[e] (δ)
1		 (0.5 h, 78%)	 (3 h, 60%)	4.12 (dd, 4 H, J = 1.6, 5.1 Hz); 5.7–5.95 (2m, 2 H)	37.9 (CH_2Cl), 129.6
2		 (0.5 h, 61%)	 (2 h, 40%)	4.49 (s, 2 H, CH_2Cl); 6.20–6.30 (m, 2 H); 7.35–7.45 (m, 1 H)	63.4 (CH_2Cl); 110.2; 109.6; 142.8; 151.8
3		 (0.5 h, 100%)	 (16 h, X = Cl: 80%[f]; X = Br: 86%[g])	X = Cl: 3.38 (s, 3 H); 4.32 (s, 2 H, CH_2Cl); 6.54 (s, 1 H); 8.07 (s, 1 H). X = Br: 3.36 (s, 3 H); 4.17 (s, 2 H, CH_2Br); 6.51 (s, 1 H); 8.07 (s, 1 H)	X = Cl: 39.8; 40.3 (CH_2Cl); 116.4; 140.0; 150.9; 162.9; 172.4. X = Br: 25.5 (CH_2Br) 39.7; 116.4; 139.9; 151.1; 163.2; 169.0
4		 (0.5 h, 95%)	 (3 h, X = Cl: 83%, X = Br: 79%, X = I: 77%)	X = Cl: 4.60 (s, 2 H, CH_2Cl); 7.30–7.45 (m, 5 H). X = Br: 4.55 (s, 2 H, CH_2Br); 7.30–7.45 (m, 5 H). X = I: 4.45 (s, 2 H, CH_2I); 7.25–7.45 (m, 5 H)	X = Cl: 46.3 (CH_2Cl); 128.4; 128.6; 128.7; 138.1. X = Br: 33.5 (CH_2Br); 128.7; 128.8; 129.4; 137.6. X = I: 5.8 (CH_2I); 127.7; 128.5; 128.6; 139.5
5		 (0.5 h, 82%)	no reaction		
6		 (4 h, 58%)	 (48 h, 82%[h])	3.14 (s, 3 H); 3.86 (s, 3 H); 4.53 (s, 2 H, CH_2Cl); 6.8–7.3 (m, 3 H)	38.3; 45.4 (CH_2Cl); 56.1; 113.0; 119.9; 124.1; 137.6; 139.9; 151.5

[a] Reaction carried out in methylene dichloride at 0 °C, except for entry 6 (room temperature). [b] Reaction carried out in DMSO at room temperature. [c] Isolated yield. [d] Spectra recorded at 200 MHz in $CDCl_3$. Chemical shift values are in ppm. [e] Spectra recorded at 50 MHz in $CDCl_3$. Chemical shift values are in ppm. [f] MS (EI): m/z 240 and 238 (M^+, 4 and 10), 175 (3), 162 (33), 160 (100), 125 (20), 79 (24). [g] MS (EI): m/z 284 and 282 (M^+, 11 and 11), 206 (5), 204 (6), 175 (7), 125 (100), 79 (60). [h] MS (EI): m/z 252 and 250 (M^+, 5 and 14), 215 (9), 173 (28), 171 (100), 137 (24).

graph (mobile phase: 100% methanol; flow rate: 1.0 mL/min; injection volume: 20 μL). Sample ionization was achieved in the filament-on mode at an electron energy of 950 eV.

General Procedure for Allyl (5*R*,6*S*)-2-(Halogenomethyl)-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylates (6–8). Methanesulfonyl chloride (75 μL, 0.97 mmol) and triethylamine (135 μL, 0.97 mmol) were added at 0 °C under nitrogen atmosphere to a solution of **3** (320 mg, 0.80 mmol) in dry methylene dichloride (5 mL). The mixture was stirred for 30 min at the same temperature, washed with aqueous 5% $NaHCO_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent gave **allyl (5*R*,6*S*)-2-[[(methylsulfonyl)oxy]methyl]-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylate (5)** (360 mg, 0.76 mmol, 94%) as a yellow oil. ^{1}H NMR: 0.06 (6 H, s), 0.87 (9 H, s), 1.23 (3 H, d, J = 6.3 Hz), 3.08 (3 H, s), 3.76 (1 H, dd, J = 1.7, 4.2 Hz), 4.15–4.32 (1 H, m), 4.58–4.80 (2 H, m), 5.20–5.45 (2 H, m), 5.18 and 5.61 (2 H, AB_q, J = 14 Hz), 5.65 (1 H, d, overlapped to AB_q lines, J not detectable), 5.80–6.02 (1 H, m). ^{13}C NMR: −5.2, −4.3, 17.9, 22.3, 25.6, 37.8 (OSO_2CH_3), 63.0, 63.8 (CH_2OSO_2), 64.9, 66.1, 72.6, 118.8, 122.4, 131.2, 147.6, 158.3, 172.7. The crude **5** was dissolved in DMSO (5 mL). A solution of the calcium halogenide (0.80 mmol) in DMSO (10 mL) was added at room temperature and the mixture stirred for 3 h at the same temperature. The mixture was diluted with ethyl acetate (15 mL) and poured into ice. The organic layer was quickly washed with cold brine and dried over Na_2SO_4. The organic solvent was evaporated to give the 2-(halogenomethyl)penems **6–8**.

Allyl (5*R*,6*S*)-2-(Chloromethyl)-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylate (6). Yield: 90%. HPLC assay: 98% (t_R = 8.4 min). ^{1}H NMR: 0.07 (6 H, s), 0.87 (9 H, s), 1.23 (3 H, d, J = 6.2 Hz), 3.73 (1 H, dd, J = 1.6, 4.3 Hz), 4.60–4.81 (2 H, m), 4.62 and 4.94 (2 H, ABq, J = 14 Hz), 5.20–5.47 (2 H, m), 5.63 (1 H, d, J = 1.6 Hz), 5.81–6.03 (1 H, m). ^{13}C NMR: −5.3, −4.7, 17.9, 22.3, 25.6, 37.6 (CH_2Cl), 62.4, 64.9, 65.8, 72.0, 118.6, 121.8, 131.2, 150.9, 158.9, 172.3. MS (EI): m/z 417 (M^+, 2), 360 (27), 234 (20), 219 (4), 218 (11), 217 (9), 143 (100).

Allyl (5*R*,6*S*)-2-(Bromomethyl)-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylate (7). Yield: 85%. HPLC assay: 98% (t_R = 12.9 min). ^{1}H NMR: 0.07 (6 H, s), 0.87 (9 H, s), 1.23 (3 H, d, J = 6.2 Hz), 3.73 (1 H, dd, J = 1.6, 4.2 Hz), 4.17–4.31 (1 H, m), 4.51 and 4.81 (2 H, ABq, J = 12 Hz), 4.59–4.82 (2 H, m), 5.20–5.47 (2 H, m), 5.62 (1 H, d, J = 1.6 Hz), 5.81–6.19 (1 H, m). ^{13}C NMR: −5.2, −4.4, 17.9, 22.3, 23.1 (CH_2Br), 25.6, 62.4, 64.9, 65.9, 72.0, 118.6, 121.8, 131.3, 150.7, 159.0, 172.1. MS (TS): m/z 494–496 (M + H^+ + MeOH, 3–4), 479–481 (M + NH_4^+, 27 and 27), 414 (m/z 494 − HBr, 10), 262–264 (37–39), 177 (100), 147 (70).

Allyl (5*R*,6*S*)-2-(Iodomethyl)-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylate (8). Yield: 75%. HPLC assay: 95% (t_R = 14.1 min). ^{1}H NMR: 0.06 (6 Hs, s), 0.87 (9 H, s), 1.23 (3 H, d, J = 6.2 Hz), 3.71 (1 H, dd, J = 1.7, 4.3 Hz), 4.18–4.30 (1 H, m), 4.50 and 4.70 (2 H, AB_q, J = 10 Hz), 4.58–4.81 (2 H, m), 5.17–5.46 (2 H, m), 5.59 (1 H, d, J = 1.7 Hz), 5.80–6.06 (1 H, m). ^{13}C NMR: −6.2 (CH_2I), −5.2, −4.3, 17.9, 22.3, 25.6, 62.2, 64.9, 65.9, 71.8, 118.6, 120.4, 131.4, 152.9, 159.3, 171.7. MS (TS): m/z 542 (M + H^+ + MeOH, 3), 527 (M + NH_4^+, 3), 399 (m/z 527 − HI, 5), 310 (41), 243 (100), 200 (20).

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Supplementary Material Available: Copies of ^{1}H NMR spectra of **4** and **6–8** and ^{13}C NMR spectra of **6–8**; procedure for preparation of **4** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.