Pergamon

Tetrahedron Letters, Vol. 35, No. 9, pp. 1417-1420, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0068-9

2-(Iodomethyl) Penems as Useful Substrates in the Wittig Olefination: Synthesis of 2-Arylethenyl Penems

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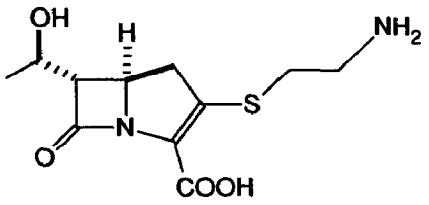
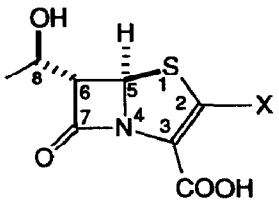
Abstract: Wittig olefination at room temperature on the new (2-iodomethyl) penems **4** gave a series of (2-arylethenyl) penems **5** with different E/Z selectivity depending on the position and electronic effect of the substituent on the aryl aldehyde.

Among the large group of novel β-lactam structures [1] described since the discovery of the natural carbapenem thienamycin **1** in 1976 [2], the highly potent, broad spectrum penem antibiotics **2** [3] still retain the unique feature of being totally synthetic ones, lacking a natural counterpart. The penem skeleton, born as a hybrid between penicillins and cephalosporins, has been the object of extensive synthetic work since its first synthesis in 1978 [4]. Substituent at C-6 is usually chosen to be 1(R)-hydroxyethyl, which is important for the antibiotic activity and stability against β-lactamases, while a large differentiation is possible in the nature of the X substituent at C-2.



1

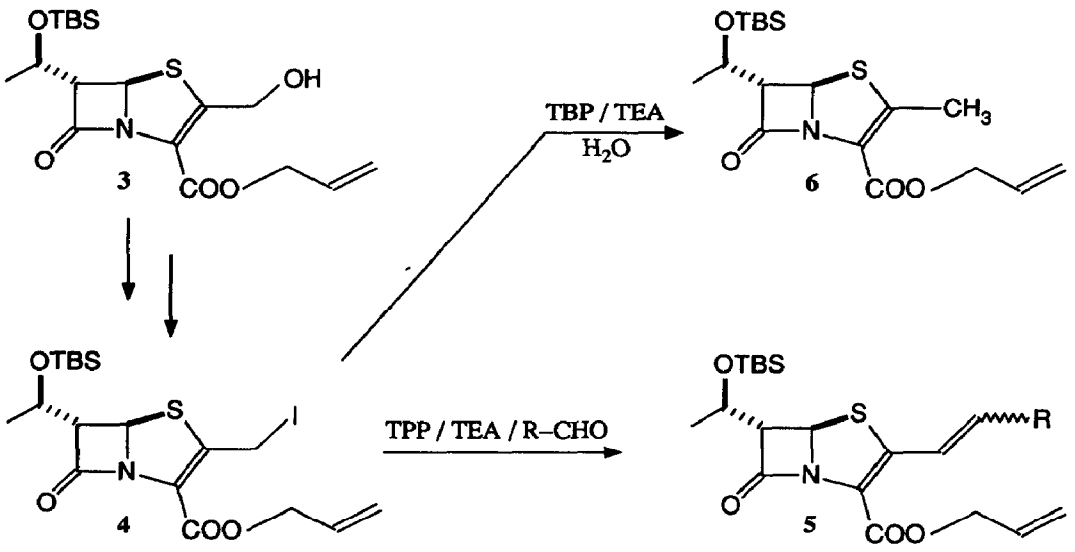


2

During our studies on new penem antibiotics with improved biological properties we became interested in the synthesis of 2-alkenyl substituted penems. The idea was that the presence of a second, conjugate double bond between the penem skeleton and the C-2 substituent could modify the reactivity and liposolubility of the penem system. Only a few general methods allowing the direct functionalization at position 2 were published in recent years [5], while most of the new penems are prepared by insertion of the right side chain on a monocyclic azetidinone followed by its conversion to the penem system by thiazoline ring construction [6]. In a recent paper we reported the first synthesis of (2-iodomethyl) penems [7]. We wish now to describe how they could represent useful intermediates for the synthesis of (2-arylalkenyl) penems by a Wittig procedure.

The extreme sensitivity of the penem nucleus to basic or acidic reagents and its low thermal stability strictly conditioned the synthetic procedure; therefore we had to find out a mild methodology for the Wittig olefination. Recently a mild procedure for the olefination at C-3 position of cephalosporins starting from a (3-iodomethyl) cephem derivative was reported [8]. This multi-step method uses sodium hydrogen carbonate in a double phase system in order to obtain the ylide from the phosphonium salt. We now report a simple one pot method for the conversion of 2-(iodomethyl) penems into the corresponding alkene derivatives, using standard conditions and triethylamine in homogeneous phase as a base to obtain the ylide from the phosphonium salt.

According to our published procedure [7], the alcohol **3** was converted into the corresponding mesylate and transformed into the halogeno derivative using CaI_2 in DMSO. Triphenylphosphine was then added to the red solution containing the 2-(iodomethyl) penem **4**; after 30 minutes at room temperature the solution turned orange and the phosphonium salt was obtained. Subsequently, triethylamine was used to obtain the corresponding ylide that reacted at room temperature with aromatic aldehydes to furnish the corresponding 2-(arylethenyl) penems **5** (Scheme 1) [9].

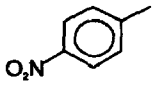
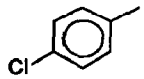
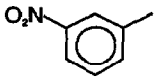
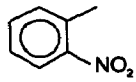
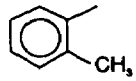
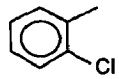


TEA = triethylamine. TBP = tri(n-butyl)phosphine. TBS = *tert*-butyldimethylsilyl. TPP = triphenylphosphine.

Scheme 1

The results are shown in Table 1. Benzaldehyde (entry 1) easily reacted to give the corresponding alkene. When the aromatic ring was substituted with electron-withdrawing groups in para position (entry 2, 3) the aldehydes resulted more reactive; consequently better yields were obtained. Furthermore good E selectivity, as expected for semistabilized ylide [10], was obtained. In the case of aldehydes bearing substituents in ortho position (entry 5 - 7) the effect of steric hindrance seems to be more important than that of the electronic properties. In fact the o-nitrobenzaldehyde (entry 5) that has a more hindered and more electron-withdrawing substituent as compared with methyl and chlorine (entry 6 and 7) gave poorer yield and a decreased reaction selectivity.

Table 1. Synthesis of 2-Alkenyl Penems **5** from **4** and Aldehydes

Entry	R	Time	Overall Yield % [a]	E/Z [b]
1		16 h	37	91/9
2		16 h	43	93/7
3		24 h	48	97/3
4		16 h	21	93/7
5		72 h	traces [c]	61/39
6		16 h	12	71/29 [d]
7		48 h	39	64/26 [d]
8	CH_3–CH_2–	0 - 72 h	no olefination	---

[a] Yield of isolated and fully characterized products. Overall yield from **3**. [b] From HPLC of crude reaction mixture. [c] Detected by HPLC (column: 10 μm C_{18} Bondclone, flow rate: 1.0 mL/min, mobile phase: 15/85 mixture of water/acetonitrile, UV monitoring : 220 and 320 nm). [d] From ^{1}H NMR of isolated products.

When aliphatic aldehydes were used, no olefination occurred and the reagents underwent a slow degradation [11]; therefore we performed the reaction using tri(n-butyl)phosphine instead of triphenylphosphine. The use of alkyl phosphines when a strongly reactive ylide is required is well documented in the literature [12]. The alkyl group on phosphorus is supposed to increase the reactivity of the ylide by stabilizing the contributing dipolar form in the resonance hybrid. However the reaction of **4** with tri(n-butyl)phosphine resulted, after aqueous work-up, only in the reduction of **4** to the 2-methyl penem **6** (42% overall yield from **3**), probably by hydrolysis of the ylide intermediate.

In summary the one-pot route to (2-arylethenyl) penems from (2-iodomethyl) penems under standard conditions, at room temperature, using a Wittig procedure has been described.

Further work is in progress on the use of ketones and alkyl aldehydes.

Acknowledgment. We wish to thank Prof. F. Arcamone and Dr. V. Pestellini for their encouraging interest in this work and for helpful suggestions. Many thanks are due to Mr. P. Sbraci for his enthusiastic technical assistance. This work was supported in part by MURST (IMI Grant No. 53529).

REFERENCES AND NOTES

1. (a) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K.H.; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180. (b) *Recent Progress in the Chemical Synthesis of Antibiotics* Lukacs, G.; Ohno, M., Eds.; Springer Verlag: Berlin-Heidelberg, 1990.
2. Ratcliffe, R.W.; Albers-Schoenberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R.B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp. 227-314.
3. (a) Perrone, E.; Franceschi, G. *Synthesis of Penems*. Reference 1b; pp. 613-704. (b) McCombie, S.W.; Ganguly, A.K. *Medicinal Research Reviews* **1988**, *8*, 393.
4. Ernest, I.; Gosteli, J.; Greengrass, C.W.; Holick, W.; Jackman, D.E.; Pfaendler, H.R.; Woodward, R.B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.
5. Wild, H. In *The Organic Chemistry of β-Lactams*; Georg, G. I. Ed.; VCH Publishers: New York, 1993; pp. 96-105.
6. Cabri, W.; Zarini, F.; D'Anello, M.; Marchi, M.; Bedeschi, A.; Franceschi, G. *Tetrahedron Lett.* **1993**, *34*, 3491-3492.
7. We reported the complete experimental procedure and spectroscopic characterization of 2-(chloromethyl)-, 2-(bromomethyl) and 2-(iodomethyl) penems in: Altamura, M.; Perrotta, E. *J. Org. Chem.* **1993**, *58*, 272.
8. Pitlik, J.; Batta, G.; Sztaricskai, F. *Liebigs Ann. Chem.* **1992**, 895-898.
9. **Allyl (5*R*,6*S*)-2-(p-Nitrophenylethenyl)-6-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]penem-3-carboxylate. (Typical procedure).** To a stirring, red solution of **4** obtained from **3** (200 mg, 0.50 mmol), in DMSO (5 mL), at room temperature, triphenylphosphine (131 mg, 0.50 mmol) was added. After 30 min at room temperature the solution turned orange. Triethylamine (85 μL, 0.61 mmol) was added, followed after 30 min by 4-nitrobenzaldehyde (91 mg, 0.60 mmol). After 16 h the solution was diluted with ethyl acetate and poured into water. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and column chromatography on silica gel (cyclohexane/ethyl acetate 3:1 v/v) gave 112 mg of wax product (43% overall yield from **3**). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.10 (6 H, s), 0.90 (9H, s), 1.28 (3 H, d, J = 6.2 Hz), 3.60 (1 H, dd, J = 1.7, 3.9 Hz, Z isomer), 3.75 (1 H, dd, J = 1.7, 4.4 Hz, E isomer), 4.16-4.38 (1 H, m), 4.65-4.86 (2 H, m), 5.20-5.50 (2 H, m), 5.61 (1 H, d, J = 1.7 Hz), 5.84-6.10 (1 H, m), 6.77 (1 H, d, J = 16 Hz, E isomer), 6.88 (1 H, d, J = 12 Hz, Z isomer), 7.35 (1 H, d, J = 12 Hz, Z isomer), 7.62 (2 H, d, J = 9 Hz), 8.19 (1 H, d, J = 16 Hz, E isomer), 8.20 (2H, d, J = 9 Hz). Ms(EI): m/z 516 (M^+, 2), 459 (26), 316 (100).
10. Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis* ; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol.1, pp 775-782 and references cited therein.
11. As the reaction was carried on for several hours in a polar solvent under basic conditions, aldol condensation could not be excluded.
12. Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: London, 1979; pp 20-23.

(*Received in UK* 27 *October* 1993; *revised* 23 *December* 1993; *accepted* 7 *January* 1994)