J.Sci.I.R.Iran

Vol. 1, No. 5
Autumn, 1990

2-DIMETHYLPHOSPHONO-(3-METHOXYCARB-ONYL)-6-PHENYLACETAMIDO CARBAPENAM

G.H.Hakimelahi and A.A. Jarrahpour

Department of Chemistry, Faculty of Science, University of Shiraz, Shiraz
Islamic Republic of Iran

Abstract

The title compound has been synthesized starting from cis- N- (α-methylacrylyl) -3-N- Phenylacetamido -4- styryl -2- azetidinone (1) [1].

Introduction

As part of a program to synthesize classical and nonclassical ß- lactam antibiotics, we were interested in developing a method to prepare a carbapenam derivative **7**, bearing at the 2- position a phosphonate function, which might exhibit interesting antimicrobial activity and serve as a precursor for the synthesis of many ß- lactam derivatives including compounds such as Δ^{2-} carbapenem **8**.

A solution of **1** in tetrahydrofuran (THF) was treated with two equiv. of dimethyl phosphite and one equiv. of sodium hydride to give the adduct **2**. Ozonolysis of **2** and subsequent treatment of the ozonide intermediate with dimethyl sulfide at -70 to 20°C gave aldehyde **3** (80%) characterized by its elemental analysis, IR., NMR., and chemical ionization mass spectra (CI.-MS.). All attempts to prepare Δ^{1} carbapenem **4** failed and resulted in recovery of the starting material **3**. At this point it was decided to prepare Δ^{2-} carbapenem **8** via the synthesis of carbapenam **7** precursor. The aldehyde **3** could be cleanly converted to the alcohol **5** (90%) by means of sodium borohydride in methanol at O°C [2]. Treatment with trifluoromethanesulfonyl chloride in the presence of triethlamine in methylene chloride gave triflate **6** (60%). Attempts to cyclize **6** **in refluxing benzene containing triethylamine failed. Attempted conversion of the triflate to their respective iodide using sodium** Iodide **in acetone or t-n-butylammonium iodide in refluxing benzene failed [3]. Successful cyclization could be achieved when triflate 6** was treated with two equiv. of n-BuLi in THF at- 28°C for **5** h, in which case 20% of cyclization product **7** was isolated. All attempts to transform **7** ⟶ **8**, through an elimination reaction, failed and resulted in recovery of the starting material or destruction of the ß-lactam ring.

Key words: Carbapenam, ß - lactam

Experimental Section

General procedure: See ref. 4.

Preparation of methyl 2-(2-Oxo-3-phenylacetamido - 4- styryl- 1- azetidinyl) -2- dimethyl phosphonatopropionate (2). To a solution of **1** (5 mmol) and dimethyl phosphite (10 mmol) in 50 ml THF, NaH (5 mmol, washed with THF) was added at 0°C. After stirring for 1h, and evaporation to dryness, the residue was dissolved in ether, washed with water and dried ($MgSO_4$). Filtration and evaporation gave a quantitative yield of **2** as a oil. Purification by column chromatography using silica gel, and elution with AcOET gave (85%) of **2** as a foam. NMR. ($CDCl_3$): δ 7.78 (d, lH, NH), 7.39 (s, 5H, Ph-C = C), 7.00 (s, 5H, Ph), 5.88- 6.91 (m, 2H, CH = CH), 5.51 - 5.69 (m, lH, H-C (3)), 4.63 (br. lH, H-C (4)). 4.51 (m, lH, CHCOO), 3.65 - 4.21 (m, 9H, 3Me), 3.46 (s, 2H, CH_2Ph), 2.41 (m, 2H, CH_2P). IR. (CH_2Cl_2): 3420 (NH), 1760 (ß-lactam), 1740 (ester), 1681(amide)cm^{-1}

Preparation of methyl 2-(2-Oxo-3-Phenylacetamido -4- trifluoromethane sulfonyloxymethyl- 1- azetidinyl) - 2- dimethylphosphonatopropionate (6). Ozone was passed for 2 h through a solution of **2** (5g) in CH_2Cl_2 (100 ml) at-78°C. After purging with N_2, dimethyl sulfide (3 equiv.) was added and the solution was

allowed to warm to 25°C (2 h). The solvent was evaporated and the resulting compound **3** was dissolved in 100 ml MeOH. $NaBH_4$ (5 equiv.) was added at 0°C. After 1 h 5 ml 10% HCL was added. The solution was evaporated to 50 ml, diluted with water, and was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and evaproated to give crude product. Purification on silica gel and elution with ethyl acetate gave 90% yield of alcohol **5**. Reaction of **5** (0.01 mol) with trifluoromethanesulfonyl chloride (0.01 mol) and triethylamine (0.015 mol) in methylene chloride (50 ml) gave, after aq. work up, **6** which was purified on silica gel using chloroform as eluent (60%). NMR. ($CDCl_3$): δ 7.77 (d, lH, NH), 7.20 (s, 5H, Ph), 5.53 - 5.71 (m, 1H, H-C (3)), 4.41 (br. m, lH, H-C (4)), 4.81 (br., 2H, CH_2O), 4.51 (m, lH, CHCOO), 3.65 - 4.30 (m, 9H, 3Me), 3.46 (s, 2H, CH_2Ph), 2.42 (m, 2H, CH_2P). IR. (CH_2Cl_2): 3410 (NH), 1780 (ß-lactam), 1745 (ester), 1680 (amide) cm^{-1}.

Preparation of 2-dimethylphosphono- (3- methoxycarbonyl) -6- phenylacetamido carbapenam (7). To a stirred solution of phosphoate **6** (0.01 mol) in 20 ml of dry THF a solution of n-butyllithium (0.01 mol) in hexane was added dropwise under an argon atmosphere at -28°C. The solution was stirred at the same temperature and allowed to warm to 25°C within 3 h. The solution was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated to afford compound **7**. Purification on silica gel and elution with ethyl acetate/ chloroform (1:1) gave pure **7** (20%) NMR. ($CDCl_3$): δ 7.76 (d, 1H, NH), 7.35 (s, 5H, Ph), 5.13 (m, 1H, *CH*NH), 4.53 (br. m, 1H, CHN), 4.62 (m, 1H, CHCOO), 3.60 - 4.40 (m, 9H, 3Me), 3.46 (br.s, 2H, CH_2Ph), 2.56 (m, 1H, CHP), 1.49 (m, 2H, CH_2CP). IR. (CH_2Cl_2): 3405 (NH), 1789 (ß-lactam), 1740 (ester), 1682 (amide) cm^{-1}. CI.- MS. 411 ($M^+ + 1$). $C_{18}H_{23}N_2O_7P$ (410.45): Calc. C 52.68, H 5.60, N 6.80%. Found: C 52.62, H 5.63 N 6.82%.

Acknowledgement

We wish to thank the Shiraz University Research Council for financial support and Mr. Ketabchi for technical assistances.

References

1. G. Just, and T. J. Liak, *Can. J. Chem.* **56**, 211 (1978).
2. G. H. Hakimelahi, and G. Just, *ibid.* **57**, 1932 (1979).
3. T. W. Doyle, B. Yuluh, D. T. Wuchu, and B. Belleau, *ibid.* **55**, 2719 (1977).
4. G. H. Hakimelahi, C. B. Boyce, and H. S. Karmia, *Helv. Chim. Acta* **60**, 342 (1977).