Notes

Phosphorodimorpholidic Halides as a New Condensing Reagent for the Formation of β-Lactams from β-Amino Acids

Young Haeng Lee, Hyun Chul Kim, and Chai-Ho Lee

Department of Chemistry, Wonkwang University, Iksan 570-749, Korea

Received October 10, 1995

Phosphorochloridate and phosphoramidic halide have been known to phosphorylate the alcohol in presence of an organic base and thus applied to the synthesis of monophosphate esters.[1] Among many phosphorylating reagents, phenyl phosphorodichloridate has found wide application in most organic transformations.[2] Similar reagents, such as diphenyl phosphorochloridate, N,N-dimethylphosphoramidic dichloride[3] and N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride have also been used for the synthesis of amides,[3] esters,[4] carboxylic acid anhydrides[5] and for the conversion of β-amino acids into β-lactams.[6]

In connection with the β-lactam chemistry undergoing in this laboratory, we have examined the effectiveness of phosphoramidic halide reagents derived from morpholine. After much experimentation, phosphorodimorpholidic bromide (**3a**) and phosphorodimorpholidic chloride (**3b**) have been found to be very effective in promoting β-lactam formation from β-amino acids. Phosphorodimorpholidic chloride (**3b**) and phosphorodimorpholidic azide (**5**) gave similar results but they were less effective than phosphorodimorpholidic bromide. Phosphorodimorpholidic halide reagents can be easily prepared by the reaction of morpholine (**1**) with phosphorous oxyhalide (**2a** or **2b**) in chloroform or benzene for 4 h at 10 ℃. Phosphorodimorpholidic azide was conventiently obtained by the reaction of phosphorodimorpholidic bromide with sodium azide in acetone at room temperature for 12 h. Phosphorodimorpholidic chloride (**3b**) was obtained as a white crystal in quantitative yield (88-90%) and can be stored in a refrigerator for several weeks without any decomposition. However, phosphorodimorpholidic bromide (**3a**) was easily decomposed by moisture within one week.

With 3-benzylaminobutanoic acid as a model substrate, several solvents such as acetonitrile, dichloromethane, N,N-dimethylformamide and tetrahydrofuran were tested under various substrate concentration at room temperature or at refluxing condition. The best result was obtained in case of the substrate concentration of 0.01 M in acetonitrile with refluxing for 12 h.

Table 1 summarizes some of experimental results and illustrates the efficiency of the present method. The cyclization reaction works well with phosphorodimorpholidic bromide (**3a**) reagent to provide good to excellent yields of the corresponding β-lactams. The reaction also works with phosphorodimorpholidic chloride (**3b**) to give moderate yields of the expected β-lactams. Particularly, phosphorodimorpholidic azide (**5**) give poor results due to the poor leaving power of its azido group.

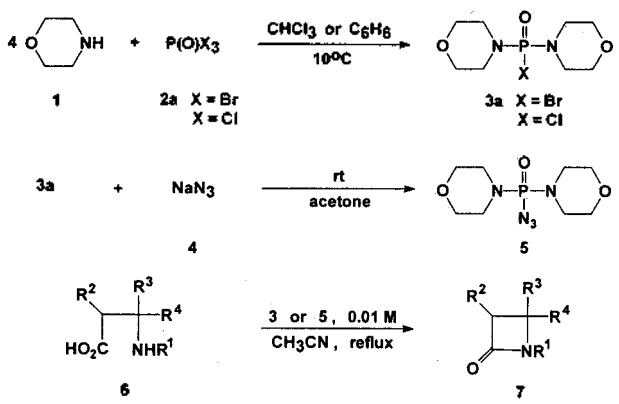


Table 1. Synthesis of β-Lactams from β-Amino Acids

β-Amino acids				Yield (%) of β-Lactams[a]		
R^1	R^2	R^3	R^4	3a	3b	3c
$PhCH_2$	H	CH_3	H	84	70	28
$PhCH_2$	H	CH_3	CH_3	91	80	
$PhCH_2$	H	CH_2CH_3	H	83		25
$PhCH_2$	CH_3	H	H	90	79	30
$PhCH_2CH_2$	H	CH_3	CH_3	85		
$C_6H_3(OCH_3)_2CH_2$[b]	H	CH_3	H	82	80	76
H	H	CH_3	H	70		
H	H	Ph	H	72		

[a] Isolated yields by flash column chromatography. [b] 3,4-Dimethoxybenzyl.

In conclusion, the reagents (**3a, 3b**) are readily available and applicable to the β-amino acids of which the amino group is primary.

Experimental

IR spectra were recorded on a JASCO FT-IR-5300 spectrometer, ^{13}C NMR spectra were recorded on a Bruker AC 200F (200 MHz) spectrometer with $CDCl_3$ as solvent tetramethylsilane as internal standard. Melting points were determined with Buchi 510 apparatus and were uncorrected. Flash column chromatography was performed using E. Merck Kiesegel 60 (230-400 mesh) silica gel.

Preparation of phosphorodimorpholidic bromide (3a). Morpholine (3.50 g, 0.04 mol) gradually added to phosphorus oxybromide (2.90 g, 0.01 mol) in chloroform (30 mL) at 10 ℃. The mixture was stirred at room temperature for 4 h, filtered and evaporated. The resulting white solid used directly for condensing reagent. Yield 88-90%, mp 77-79 ℃, ^{13}C NMR (200 MHz, $CDCl_3$) δ 44.45, 66.78.

Preparation of phosphorodimorpholidic chloride (3b). Compound **3b** was prepared from morpholine (**1**) and

phosphorus oxychloride (**2b**) with benzene as described above. Yield 85-87%, mp 80-81 ℃.

Preparation of phosphorodimorpholidic azide (5). A mixture of phosphorodimorpholidic bromide (**3a**) (2.89 g, 0.01 mol) and sodium azide (0.65 g, 0.01 mol) in acetone (20 mL) was stirred at room temperature for 20 h. The mixture was filtered and evaporated to give the **5**. Yield 70-75%, mp 36-38 ℃; IR(KBr) 2854, 2760, 2148, 1257 cm^{-1}.

A typical procedure for β-lactams from β-amino acids is as follow. To a suspended solution of 3-benzylamino-3-methylbutanoic acid (207 mg, 1.0 mmol) and phosphodimorpholidic bromide (360 mg, 1.2 mmol) in acetonitride (100 mL) was added triethylamine (120 mg, 1.2 mmol) at room temperature. After being stirred at 80 ℃ for 15 h, the reaction mixture was concentrated under reduced pressure and the residue was pass through flash chromatography column using ether-chloroform (2 : 1) as an eluent to yield 1-benzyl-4,4-dimethyl-2-azetidinone (172 mg, 91%) as an oil.

Acknowledgment. This work was supported by the Basic Research Institute Program, Ministry of Education (BSRI-95-3431).

References

1. (a) Montgomery, H. A. C.; Turnbull, J. H. *J. Chem. Soc.* **1958**, 1963. (b) Khwaja, T. A.; Reese, C. B.; Stewart, J. C. M. *J. Chem. Soc. (C)*, **1970**, 2092. (c) Khwaja, T. A.; Reese, C. B. *Tetrahedron* **1971**, *27*, 6189.
2. (a) Arrieta, A.; Garcia, T.; Lago, J. M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471. (b) Lago, J. M.; Palomo, C. *ibid.* **1983**, *13*, 653. (c) Liu, H. J.; Nyangulu, J. M. *Tetrahedron Lett.* **1988**, *29*, 3167. (d) Liu, H. J.; Lamoreux, M.; Llinas-Brunet, M. *Can. J. Chem.* **1986**, *64*, 520.
3. Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, J.; de Retana, A. O.; Cuevas, C. *J. Org. Chem.* **1991**, *56*, 2244 and the references cited therein.
4. Diago-Meseguer J.; Palomo-Coll, A. L. *Synthesis.* **1980**, 547.
5. Cabre-Castellvi, J.; Palomo-Coll, A.; Palomo-Coll, A. L. *Synthesis* **1981**, 616.
6. Chung, B. Y.; Goh, W.; Nah, C. S. *Bull. Korean Chem. Soc.* **1991**, *12*, 457.

Isolation and Characterization of Oxochromium (IV) Tetraphenylporphyrin Pyridine Complex and Its Derivatives

Rizhen Jin, Chan Sik Cho, Li Hong Jiang, and Sang Chul Shim*

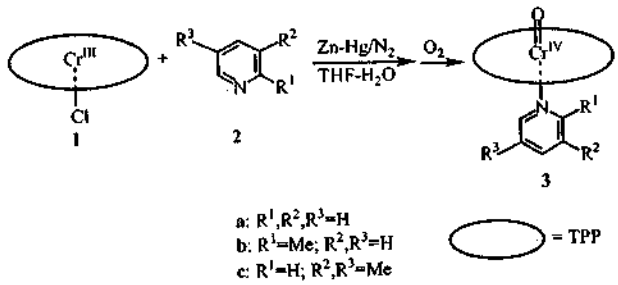
Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea

Received January 22, 1996

Cytochrome P-450 enzymes selectively oxidize hydrocarbons through the activation of molecular oxygen in the biosphere.[1] It has been proposed that the activation of oxygen by cytochrome P-450 enzymes involves oxoiron porphyrin intermediate.[2] Free oxoiron porphyrins, which are unstable above −30 ℃, are only studied in solution. While several oxometal porphyrins such as those of titanium(IV),[3] vanadium (IV),[4] molybdenum(IV and V),[5,6] and chromium(IV)[7,8] have been isolated and characterized, these compounds have not been shown to be effective oxidizing agents. The oxometal porphyrins such as those of chromium(V)[9] and manganese (IV)[10,11] have been shown to be effective oxidizing agents, but they were not synthesized through the activation of molecular oxygen. We report here the synthesis, isolation and spectral characterization of oxochromium(IV) tetraphenylporphyrin pyridine complex and its derivatives through the activation of molecular oxygen. The complexes are capable of oxidizing cyclohexene and styrene at room temperature to give 2-cyclohexen-1-ol and styrene oxide, respectively. They could be regarded as a model of the active oxygen species generated at the cytochrome P-450 catalytic center.

Results and Discussion

Reduction of ClCr(III)TPP in the mixture of tetrahydrofuran, pyridine derivatives, and water by activated zinc under nitrogen followed by stirring under air led to the isolation of a crystalline blackish green oxochromium(IV) complexes **3a-c** in 60, 63, and 61% yields, respectively (Scheme 1).[12] Elemental analyses of the oxochromium(IV) complexes **3a-c** were consistent with compounds for the formula oxochromium(IV) tetraphenylporphyrin pyridine complex and its derivatives. The visible spectra of **3a-c** display an intense Soret band at 430 nm and a broad shoulder band at 540 nm. The



Scheme 1.