

HIGHLY EFFICIENT OXAZOLONE-DERIVED REAGENTS FOR BETA-LACTAM FORMATION FROM BETA-AMINO ACIDS

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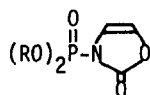
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Summary: Based on a unique leaving ability of 2-oxazolone moiety, highly efficient reagents have been developed for the formation of β -lactam compounds from β -amino acids including a facile preparation of the penam, a basic skeleton of penicillins.

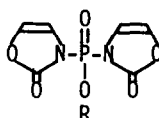
Continuing work on the 2-oxazolone chemistry has revealed that 2-oxazolone moiety has synthetic potential as a unique leaving group in carboxyl¹⁾ and phosphoryl activating processes.²⁾ This paper describes further utility of such a simple heterocycle which plays an important role in a facile preparation of β -lactam compounds from β -amino acids.

There have appeared a substantial number of methods for the constructions of β -lactam rings³⁾ due to great interests in the β -lactam antibiotics, the most widely prescribed drugs in therapy. There still exist ongoing needs to develop general and effective methods for smooth cyclization of β -amino acids to β -lactams, since the conventional reagents such as DCC,⁴⁾ SOCl_2 ,⁵⁾ and bis-(5-nitro-2-pyridyl) trichloroethyl phosphate⁶⁾ have some limited use as partly pointed out.^{7,8)} Among the methods available, the Mukaiyama-Ohno's procedure using triphenylphosphine/2,2'-dipyridyl disulfide in acetonitrile⁷⁾ might be most versatile and has been widely employed for such condensations. Application of this method to 2-thiazolidineacetic acid was not promising and resulted in poor yield (8%) of the penam, a basic skeleton of penicillin-type β -lactams.⁹⁾

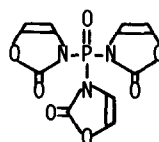
So, the phosphorus compounds $\mathbf{1}$ - $\mathbf{3}$ activated by 2-oxazolone moiety were systematically examined as condensing reagents for the formation of β -lactam compounds from free β -amino acids, since we previously recognized the usefulness of these types of reagents in peptide¹⁾ and thioester¹⁰⁾ synthesis as well as β -lactam formation.¹¹⁾ Compounds studied in this work involve diphenyl 2-oxo-3-oxazolinylphosphonate ($\mathbf{1}$: R=Ph),¹⁾ p-chlorophenyl bis(2-oxo-3-oxazolin-



(1)



(2)



(3)

yl)phosphinate ($\mathbf{2}$; $R=p\text{-Cl-Ph}$)²⁾ and tris(2-oxo-3-oxazolinyl)phosphine oxide ($\mathbf{3}$). These reagents are readily obtainable from 2-oxazolone and the corresponding halogenophosphorus compounds in the presence of bases and the crystalline agents thus obtained are equally stable enough to be stored in a desiccator for months without any practical decompositions. Thus, in analogy with compound $\mathbf{1}$ and $\mathbf{2}$, the tris-oxazolidine $\mathbf{3}$ (mp 167°, $^1\text{H-NMR}$ δ 7.30-7.52 (m)) was prepared in 77% yield as colorless crystals on treatment of 2-oxazolone with phosphoryl chloride in the presence of triethylamine.¹²⁾

When β -amino acids ($\mathbf{4}$) were treated with equimolar amounts of the condensing reagents ($\mathbf{1}$, $\mathbf{2}$ or $\mathbf{3}$) in boiling acetonitrile in concentration of 10^{-2}M , cyclization smoothly proceeded to give high to excellent yields of monocyclic N-substituted and unsubstituted β -lactams ($\mathbf{5}$). The results are summarized in

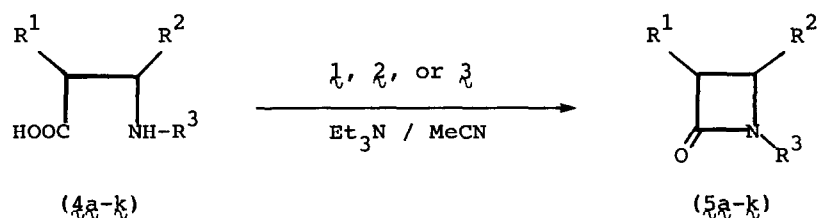


Table 1. As indicated, compound $\mathbf{3}$ is the most powerful dehydrating reagent and mono-oxazolidine $\mathbf{1}$ appears to be rather less effective. A typical procedure is given as follows. A mixture of N-benzyl- β -alanine (1 mmol), the reagent $\mathbf{3}$ (1 mmol) and Et_3N (6 mmol) in CH_3CN (100 ml) was heated under reflux for 6h. Removal of the solvent in vacuo, followed by chromatographic purification on silica gel ($\text{CH}_2\text{Cl}_2\text{-EtOAc}$) gave N-benzyl-2-azetidinone ($\mathbf{5a}$) in 96% yield. The use of smaller amounts of base (2 - 3 mmol) is preferable in cyclization with reagents $\mathbf{1}$ and $\mathbf{2}$. The 2-oxazolone heterocycle is readily water-soluble and this can greatly simplify the procedures to separate β -lactam compounds from the reaction mixture.

We next applied the present method to the synthesis of the β -lactam skeleton of penicillins, 4-thia-1-azabicyclo[3.2.0]heptan-7-one ($\mathbf{7}$) (penam), which had been attained only in a poor yield (8%).⁹⁾ Thus, a solution of 2-thiazolidineacetic acid ($\mathbf{6}$) in acetonitrile was treated with reagents $\mathbf{2}$ and $\mathbf{3}$ to give 30% and 57% yields of the penam,¹³⁾ respectively, under the same conditions as above, while reagent $\mathbf{1}$ was completely unreactive.

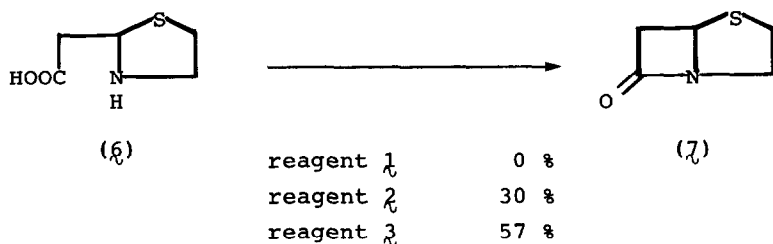


Table 1. Preparation of Monocyclic β -Lactams^{a)}

β -amino acid (4)	R ¹	R ²	R ³	β -lactam (5)	Isolated Yield		
					1	2	3
4a	H	H	CH ₂ Ph	5a	85 %	87 %	96 %
4b	CH ₃	H	CH ₂ Ph	5b	88	92	93
4c	H	CH ₃	CH ₂ Ph	5c	89	85	95
4d (S)	H	COOCH ₃	CH ₂ Ph	5d (S)	52	71	82
4e (S)	H	CH ₂ COOCH ₃	CH ₂ Ph	5e (S)	75	81	87
4f	H	CH ₃	CH ₂ CH ₂ Ph	5f	74	86	88
4g	H	CH ₃	n-Pro	5g	60	73	84
4h	H	CH ₃	n-Bu	5h	63	76	85
4i	CH ₃	H	H	5i	53	73	75
5j	H	CH ₃	H	5j	57	80	80
5k	H	Ph	H	5k	50	75	88

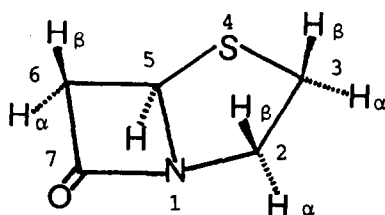
a) The reactions were carried out in boiling CH₃CN for 6h on a 1 - 3 mmol scale of β -amino acids in concentration of 10⁻² M. The β -lactam compounds described here were fully characterized by direct comparison with the authentic samples^{6-8,14)} and/or spectral analysis.¹⁵⁾

In conclusion, the present reagents, particularly 2 and 3, have the advantageous features of high yields, simple working procedures and a wide applicability, which permit the practical synthesis of the penam itself, besides good stability on prolonged storage. Further utility of the reagents as dehydrating and condensing agents is being explored.

References and Notes:

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- 12) Reagent 3 was routinely obtained in practically pure forms by washing the precipitates deposited with hot CH_2Cl_2 .
- 13) For this cyclization, reagents DCC and $\text{SOCl}_2/\text{Et}_3\text{N}$ were reported to be ineffective and $\text{Ph}_3\text{P}/(2\text{-PyS})_2$ was of limited value, yielding the penam in 8% yield.⁹⁾ The penam structure (7) was fully characterized by spectral (MS and $^1\text{H-NMR}$ ¹⁶⁾) analyses. Ms, $m/z(M^+)$ calcd 129.0248, obsd 129.0265.



(7)

$^1\text{H-NMR}$ (400 MHz, CDCl_3), δ 2.90 (ddd, 1H, $J_{2\alpha,2\beta}=12.10\text{Hz}$, $J_{2\alpha,3\alpha}=6.60\text{Hz}$, $J_{2\alpha,3\beta}=6.96\text{Hz}$, 2-H α), 2.96 (dd, 1H, $J_{5,6\beta}=1.47\text{Hz}$, $J_{6\alpha,6\beta}=15.76\text{Hz}$, 6-H β), 3.20 (ddd, 1H, $J_{2\beta,3\alpha}=6.60\text{Hz}$, $J_{2\alpha,3\alpha}=3.30\text{Hz}$, $J_{3\alpha,3\beta}=11.00\text{Hz}$, 3-H α), 3.29 (ddd, 1H, $J_{2\alpha,3\beta}=6.96\text{Hz}$, $J_{2\beta,3\beta}=6.60\text{Hz}$, $J_{3\alpha,3\beta}=11.00\text{Hz}$, 3-H β), 3.53 (dd, 1H, $J_{5,6\alpha}=4.03\text{Hz}$, $J_{6\alpha,6\beta}=15.76\text{Hz}$, 6-H α), 4.15 (ddd, 1H, $J_{2\alpha,2\beta}=12.10\text{Hz}$, $J_{2\beta,3\alpha}=3.30\text{Hz}$, $J_{2\beta,3\beta}=6.60\text{Hz}$, 2-H β), 4.96 (dd, 1H, $J_{5,6\beta}=1.47\text{Hz}$, $J_{5,6\alpha}=4.03\text{Hz}$, 5-H). Assignments for the

C-2 protons were tentatively made on the basis of the data reported (R. Busson and H. Vanderhaeghe, J. Org. Chem., 41, 2561, (1976)).

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- 15) $^1\text{H-NMR}$ (60 MHz, CDCl_3), δ 1.14 (d, 3H, $J=6.2\text{Hz}$), 2.35 (dd, 1H, $J=2.2\text{Hz}$, $J=14.3\text{Hz}$), 2.65 - 3.84 (m, 6H), 7.20 (br, s, 5H); δ 0.93 (t, 3H, $J=7.3\text{Hz}$), 1.30 - 1.90 (m, 2H), 1.32 (d, 3H, $J=5.9\text{Hz}$), 2.48 (dd, 1H, $J=2.2\text{Hz}$, $J=14.3\text{Hz}$), 2.68 - 3.45 (m, 3H), 3.51 - 3.92 (m, 1H); δ 0.92 (t, 3H, $J=7.3\text{Hz}$), 1.31 (d, 3H, $J=5.9\text{Hz}$), 1.18 - 1.72 (m, 4H), 2.43 (dd, 1H, $J=2.2\text{Hz}$, $J=14.3\text{Hz}$), 2.78 - 3.36 (m, 3H), 3.41 - 3.86 (m, 1H).
- 16) There are apparent discrepancies between the present data and the reported.⁹⁾

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