Communications to the Editor

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ARYL BIS(2-OXO-3-BENZOXAZOLINYL)PHOSPHINATE AND TRIS(2-OXO-3-BENZOXAZOLINYL)PHOSPHINE OXIDE: NEW CONDENSING REAGENTS FOR BETA-LACTAM FORMATION FROM BETA-AMINO ACIDS

Tomohisa Nagamatsu and Takehisa Kunieda*
Faculty of Pharmaceutical Sciences, Kumamoto University,
5-1, Oe-honmachi, Kumamoto 862, Japan

Beta-lactam compounds including the penam, a basic skeleton of penicillins, are conveniently prepared by the dehydration of β-amino acids using new condensing reagents which are titled.

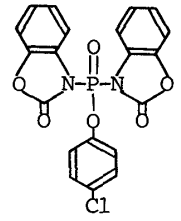
KEYWORDS ——— β-lactam; β-amino acid; penam; condensing reagent; 2-benzoxazolinone; 4-chlorophenyl bis(2-oxo-3-benzoxazolinyl)phosphinate; tris(2-oxo-3-benzoxazolinyl)phosphine oxide

Among the synthetic methods for β-lactam compounds of biological interests, intramolecular cyclization of β-amino acids is a versatile and fundamental methodology.[1] Several condensing reagents have been reported such as DCC,[2] Ph_3P/$(2\text{-PyS})_2$,[3] 2-halo-1-methylpyridinium iodide,[4] and bis(5-nitro-2-pyridyl)trichloroethyl phosphate.[5] Some of these are highly effective for β-lactam formation only in a limited number of cases.

Recent work on the use of 2-oxazolone heterocycle in the synthesis revealed that phosphorus compounds activated by such a simple heterocycle were highly promising for β-lactam formation from a wide variety of β-amino acids.[6] Such desirable results prompted us to examine the compounds activated by the 2-benzoxazolinone moiety, aryl bis(2-oxo-3-benzoxazolinyl)phosphinate (1)[7] and tris(2-oxo-3-benzoxazolinyl)phosphine oxide (2), as condensing reagents for β-lactam formation via intramolecular dehydration of β-amino acids.

As in the preparation of the bis-benzoxazolide 1 (mp 168°C) originally developed for the phosphorylation of alcohols,[7] tris-compound 2 (mp 252°C) was easily obtained in 78% yield on treatment of commercially available 2-benzoxazolinone with phosphoryl chloride in the presence of triethylamine.[8] These reagents are readily purified by chromatography on silica gel and/or recrystallization from methylene chloride-cyclohexane, and are stable enough on prolonged storage in a desiccator.

When N-substituted and non-substituted β-amino acids were treated with reagent 1 or 2 in the presence of triethylamine in boiling acetonitrile, monocyclic β-lactams were equally formed in high yields as indicated in Table I. A typical reaction procedure is as follows. A mixture of N-benzyl-β-alanine (1 mmol), the

(1) 

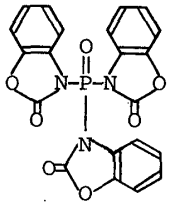
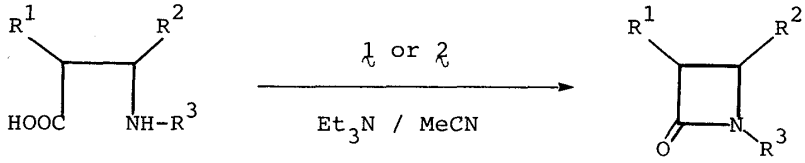
(2) 

Table I. Preparation of Monocyclic β-Lactams from β-Amino Acids[a)]



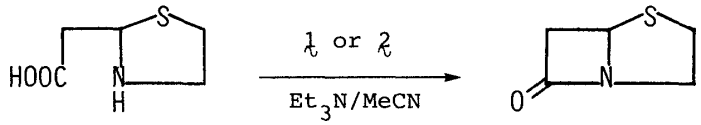
(3) (4)

β-Amino acid (3)	R^1	R^2	R^3	β-Lactam (4)	Isolated yield 1	Isolated yield 2
3a	H	H	CH_2Ph	4a	85 %	88 %
3b	CH_3	H	CH_2Ph	4b	85	87
3c	H	CH_3	CH_2Ph	4c	82	80
3d (S)	H	$COOCH_3$	CH_2Ph	4d (S)	63	76
3e (S)	H	CH_2COOCH_3	CH_2Ph	4e (S)	75	78
3f	H	CH_3	CH_2CH_2Ph	4f	77	78
3g	H	CH_3	n-Pro	4g	70	74
3h	H	CH_3	n-Bu	4h	67	75
3i	CH_3	H	H	4i	68	71
3j	H	CH_3	H	4j	76	67
3k	H	Ph	H	4k	76	72

a) All β-lactam compounds described here gave spectral data identical with those of the authentic samples.[3-6,10)]

reagent 1 (1 mmol) and triethylamine (2 mmol) was heated in acetonitrile (100 ml) under reflux for 6 h. Evaporation of the solvent in vacuo, followed by chromatographic purification on silica gel (methylene chloride-ethyl acetate) gave N-benzyl-2-acetidinone (4a) in 85% yield. The use of three eq of triethylamine is preferable in the dehydration with tris-reagent 2 which gives slightly higher yield.

This method was used to synthesize the basic skeleton of penicillin-type β-lactams, 4-thia-1-azabicyclo[3.2.0]heptan-7-one (penam) (6), for which efficient reagents had not been reported[9)] except tris(2-oxo-3-oxazolinyl)phosphine oxide quite recently developed.[6)] Thus, the suspension of 2-thiazolidineacetic acid (5) hydrochloride[9)] (1 mmol) and the reagent 2 (1 mmol) in acetonitrile (100 ml) was heated for 6 h in the presence of triethylamine (3.5 mmol). The usual work-up as above afforded the desired β-lactam compound 6[6)] in 41% yield. The reagent



(5) (6)

1 gave 23% yield of the penam 6 under the same conditions, while the versatile reagent $Ph_3P/(2\text{-PyS})_2$ was not so effective, yielding the penam only in 8% yield.[9] The mono-benzoxazolide, diphenyl 2-oxo-3-benzoxazolinylphosphonate,[7] had limited use only due to the remarkable dependency on the structural features of β-amino acids, and was found completely ineffective for the formation of the penam.

Thus, the condensing reagents described here provide highly promising methods for synthesis of β-lactam compounds from β-amino acids. Applications to the synthesis of penams and cephams are currently under investigation.

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8) ^{1}H-NMR (60 MHz, $CDCl_3$): δ 7.15 - 7.43 (9H, m), 7.58 - 7.83 (3H, m).
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