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

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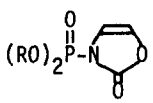
Summary: Based on a unique leaving ability of 2-oxazolone moiety, highly efficient reagents have been developed for the formation of β-lactam compounds from β-amino acids including a facile preparation of the penam, a basic skeleton of penicillins.

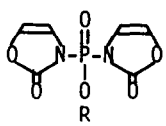
Continuing work on the 2-oxazolone chemistry has revealed that 2-oxazolone moiety has synthetic potential as a unique leaving group in carboxyl[1] and phosphoryl activating processes.[2] This paper describes further utility of such a simple heterocycle which plays an important role in a facile preparation of β-lactam compounds from β-amino acids.

There have appeared a substantial number of methods for the constructions of β-lactam rings[3] 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 phosphate[6] 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 acetonitrile[7] 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 1 - 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 peptide[1] and thioester[10] synthesis as well as β-lactam formation.[11] Compounds studied in this work involve diphenyl 2-oxo-3-oxazolinylphosphonate (1: R=Ph),[1] p-chlorophenyl bis(2-oxo-3-oxazolin-



(1)



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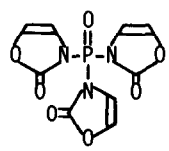
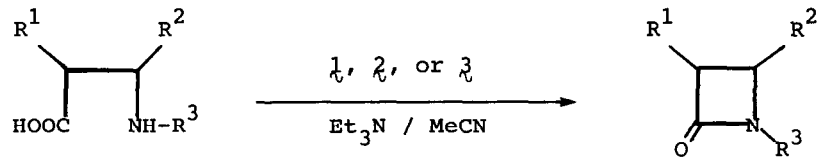


(3)

yl)phosphinate (2: R=p-Cl-Ph)[2] and tris(2-oxo-3-oxazolinyl)phosphine oxide (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 1 and 2, the tris-oxazolide 3 (mp 167°, ^{1}H-NMR δ7.30-7.52 (m)) was prepared in 77% yield as colorless crystals on treatment of 2-oxazolone with phosphoryl chloride in the presence of triethylamine.[12]

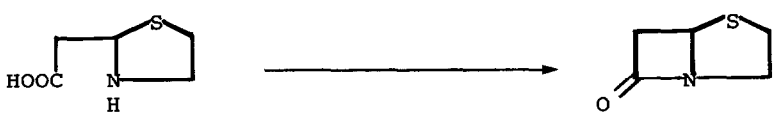
When β-amino acids (4) were treated with equimolar amounts of the condensing reagents (1, 2 or 3) in boiling acetonitrile in concentration of 10^{-2}M, cyclization smoothly proceeded to give high to excellent yields of monocyclic N-substituted and unsubstituted β-lactams (5). The results are summarized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



(4a-k) (5a-k)

Table 1. As indicated, compound 3 is the most powerful dehydrating reagent and mono-oxazolide 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 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 (CH_2Cl_2-EtOAc) gave N-benzyl-2-azetidinone (5a) in 96% yield. The use of smaller amounts of base (2 - 3 mmol) is preferable in cyclization with reagents 1 and 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 (7) (penam), which had been attained only in a poor yield (8%).[9] Thus, a solution of 2-thiazolidineacetic acid (6) in acetonitrile was treated with reagents 2 and 3 to give 30% and 57% yields of the penam,[13] respectively, under the same conditions as above, while reagent 1 was completely unreactive.



(6) (7)

reagent 1	0 %
reagent 2	30 %
reagent 3	57 %

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_2Ph	5a		85 %	87 %	96 %
4b		CH_3	H	CH_2Ph	5b		88	92	93
4c		H	CH_3	CH_2Ph	5c		89	85	95
4d	(S)	H	$COOCH_3$	CH_2Ph	5d	(S)	52	71	82
4e	(S)	H	CH_2COOCH_3	CH_2Ph	5e	(S)	75	81	87
4f		H	CH_3	CH_2CH_2Ph	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 CH_3CN 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 comparision 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 plolonged storage. Further utility of the reagents as dehydrating and condensing agents is being explored.

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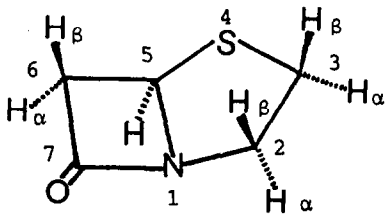
12) Reagent 3 was routinely obtained in practically pure forms by washing the precipitates deposited with hot CH_2Cl_2.

13) For this cyclization, reagents DCC and $SOCl_2/Et_3N$ were reported to be ineffective and $Ph_3P/(2\text{-PyS})_2$ was of limited value, yielding the penam in 8% yield.[9] The penam structure (7) was fully characterized by spectral (MS and ^{1}H-NMR[16]) analyses. Ms, m/z(M^+) calcd 129.0248, obsd 129.0265. ^{1}H-NMR(400 MHz, $CDCl_3$), δ 2.90 (ddd, 1H, $J_{2\alpha,2\beta}$ =12.10Hz, $J_{2\alpha,3\alpha}$=6.60Hz, $J_{2\alpha,3\beta}$=6.96Hz, 2-Hα), 2.96 (dd, 1H, $J_{5,6\beta}$=1.47Hz, $J_{6\alpha,6\beta}$=15.76Hz, 6-Hβ), 3.20 (ddd, 1H, $J_{2\beta,3\alpha}$=6.60Hz, $J_{2\alpha,3\alpha}$=3.30 Hz, $J_{3\alpha,3\beta}$=11.00Hz, 3-Hα), 3.29 (ddd, 1H, $J_{2\alpha,3\beta}$ =6.96Hz, $J_{2\beta,3\beta}$=6.60Hz, $J_{3\alpha,3\beta}$=11.00Hz, 3-Hβ), 3.53 (dd, 1H, $J_{5,6\alpha}$=4.03Hz, $J_{6\alpha,6\beta}$=15.76Hz, 6-Hα), 4.15 (ddd, 1H, $J_{2\alpha,2\beta}$=12.10Hz, $J_{2\beta,3\alpha}$=3.30 Hz, $J_{2\beta,3\beta}$=6.60Hz, 2-Hβ), 4.96 (dd, 1H, $J_{5,6\beta}$= 1.47Hz, $J_{5,6\alpha}$=4.03Hz, 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)).



(7)

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15) ^{1}H-NMR (60 MHz, $CDCl_3$), 5f:δ 1.14(d, 3H, J=6.2Hz), 2.35 (dd, 1H, J=2.2Hz, J=14.3Hz), 2.65 - 3.84 (m, 6H), 7.20 (br, s, 5H); 5g:δ 0.93 (t, 3H, J=7.3 Hz), 1.30 - 1.90 (m, 2H), 1.32 (d, 3H, J=5.9Hz), 2.48 (dd, 1H, J=2.2Hz, J= 14.3Hz), 2.68 - 3.45 (m, 3H), 3.51 - 3.92 (m, 1H); 5h:δ 0.92 (t, 3H, J=7.3 Hz), 1.31 (d, 3H, J=5.9Hz), 1.18 - 1.72 (m, 4H), 2.43 (dd, 1H, J=2.2Hz, J= 14.3Hz), 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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