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ACTIVATION OF CARBOXYL GROUPS BY DIPHENYL 2-OXO-3-OXAZOLINYLPHOSPHONATE

FACILE PREPARATION OF VERSATILE REAGENTS, 3-ACYL-2-OXAZOLONES

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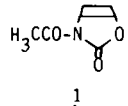
Abstract—Synthetic utility of the 2-oxazolone moiety as an excellent new leaving group is described. Based on such a function of the heterocycles, diphenyl 2-oxo-3-oxazolinylphosphonate [DPPOx] has been newly introduced as a carboxyl-activating reagent which permits a facile direct preparation of 3-acyl-2-oxazolones and amides including peptides from a wide variety of carboxylic acids. The 3-acyl-2-oxazolides also serve as versatile reactive agents for highly chemoselective acyl-transfer to the nucleophilic species such as amines, alcohols and thiols, providing convenient and high-yield routes to amides, esters and thiol esters under mild conditions. They are also useful intermediates for ketones and alcohols.

Activation of the carboxyl groups under mild conditions is apparently of great value as a fundamental process in a wide scope of chemical conversions including amide and ester formations. The 5- and 6-membered heterocycles such as imidazoles,[1] triazoles,[2] 2-thiazolidinethiones[3] and 2-pyridinethiol[4] have been successfully used in the acylation and condensation reactions as the bifunctional leaving moieties.

In connection with the synthetic applications of 2-oxazolones as a building block for amino alcohols,[5] 3-acyl-2-oxazolones (**1**) were found to undergo smooth acylation of nucleophiles such as amines and thiols under mild conditions.[6] In contrast, the structurally similar 2-oxazolidinones (**2**) showed much poorer reactivity toward benzylamine and methanol as indicated in Table 1. The reactivity of homopolymer (**3**) was intermediate between those of **1** and **2**.[7] Such observations are indicative of synthetic potential of the 2-oxazolone moiety as an excellent leaving group. It is still of interest to further explore the versatilities of the 3-acyl-2-oxazolones in acyl-transfer reactions, since there have appeared no synthetic applications of the 2-oxazolone moiety as a good leaving group, though some reactivities of the olefinic bonds of the heterocycles have been revealed by the C–C bond formations such as photo[8] and thermal cycloadditions[9] and radical oligomerizations.[5,7]

This paper describes the preparation and applications of diphenyl 2-oxo-3-oxazolinylphosphonate [DPPOx] as a new carboxyl activating reagent, which permits direct convenient preparations of amides and versatile reagents, 3-acyl-2-oxazolides, from a wide variety of carboxylic acids.[10] (Chart 1) The synthetic utility of such preservable 3-acyl-2-oxazolides may arise largely from chemo- and regioselectivity toward the acylations of polyfunctional groups as well as a facile polymerization leading to the polymeric reagents for acylation, as described elsewhere.[7]



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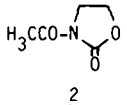

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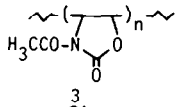

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Preparation and properties of diphenyl 2-oxo-3-oxazolinylphosphonate

Treatment of 2-oxazolone (**4**)[11] in equimolar amounts with diphenyl phosphorochloridate in the presence of base (Et_3N) gave a nearly quantitative yield of the nonirritant crystalline phosphonate [DPPOx] (**5**) (m.p. 51°), of which ^1H NMR and IR spectra showed the peaks at δ 6.74 (t) and 6.81 (d,d) (assignable to the olefinic protons) and 1788 cm^{-1} (attributable to the carbonyl function), respectively. This reagent was readily soluble in most organic solvents and highly thermostable as proved by its distillation above 200°. Good storage characteristics were shown by no virtual decompositions over dry silica gel in a prolonged storage (for years), though it underwent complete hydrolysis to diphenyl phosphate and 2-oxazolone in a 50% aqueous tetrahydrofuran solution at room temperature within 20 hr. While the DPPOx reacted with methanol only sluggishly at room temperature, the addition of the catalytic amounts of cesium fluoride caused a rapid conversion to diphenyl methyl phosphate (**7**, XR′ = OMe) quantitatively in a few minutes.[12] The replacement of the 2-oxazolone moiety by benzylamine in acetonitrile proceeded slowly at ambient temperature to give moderate yield (51%) of the phosphoramidate **7** (XR′ = $NHCH_2Ph$) over a period of a week.

Direct acylation of amines and alcohols by DPPOx

The DPPOx reagent has been preliminarily reported to be quite suitable for the efficient conversion of carboxylic acids into amides including peptides and β-lactams,[13] and thiol esters.[14]

Thus, the amido bonds were smoothly formed by treatment of carboxylic acids and amines with the DPPOx in the presence of triethylamine at room temperature. In this way, the amino protection including N-formylation and high-yield preparation of typical N-alkoxycarbonyl dipeptides (Table 2, route **a**) were readily performed. Racemization was occurred only to an extent of 3% during the coupling of N-benzyloxycarbonylglycyl-L-alanine and L-phenyl-alanine methyl ester to the tripeptide (**8**)[15] by the DPPOx–Et_3N system.

There was no difficulty in the conversions of sterically

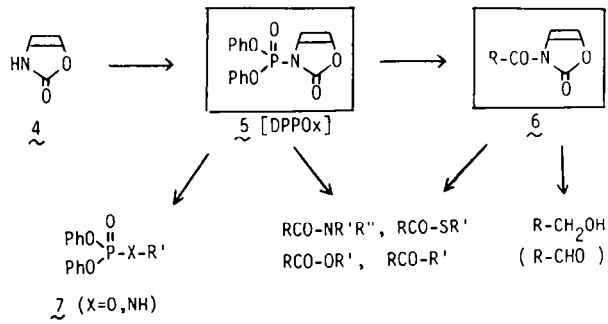


Chart 1.

Table 1. Acetylation by 3-acetyl-2-oxazolone and 2-oxazolidinone reagents[a]

Acylating Reagent :	1 ($\nu_{C=O}$ 1733 cm^{-1})[b]	2 ($\nu_{C=O}$ 1700 cm^{-1})[b]	3 ($\nu_{C=O}$ 1710 cm^{-1})[b]
$PhCH_2NH_2$[c]	98 % (5 min)	1.5 % (10 min)	40 % (10 min)
		19 (3 h)	85 (3 h)
	[91 % (0.5 h)][d]	[3.3 % (8 h)][d]	
CH_3OH[e]	98 % (10 h)	2.3 % (10 h)	

a) At room temperature. Yield and reaction time (in parentheses) are given. b) Determined in $CHCl_3$ and attributable to the acetyl groups. c) Treated with two-equimolar amounts of the reagents in CH_3CN. d) Acetylated with an equimolar reagent in benzene. e) Used as a solvent.

Table 2. Preparation of dipeptides[a]

	Yield (%) route-a	Yield (%) route-b	mp (°)	$[\alpha]_D$ (EtOH)	[lit.]
N-Cbz-L-Ala-Gly-OEt	88	98	97-99	- 22.0° (c=1)	[- 22.2°][b]
N-Cbz-L-Phe-Gly-OH		89	145-151	- 17.0° (c=1.2)	[-16.5°][c]
N-Cbz-L-Phe-Gly-OEt	83	95	106-108	- 16.8° (c=5)	[- 16.9°][d]
N-Boc-L-Phe-L-Ala-OEt	90		100-102	- 14.6° (c=2.5)	
N-Boc-L-Pro-Gly-OEt		94	oil	- 58.0° (c=7.8)	

a) In CH_3CN at room temperature. Route-a refers to a method for direct coupling of N-protected α-amino acid and amino acid ester using DPPOx (5) (1.2 equiv) in the presence of Et_3N (1.0 equiv). Route-b refers to an aminolysis of N-protected amino acid oxazolides (6h-k) with free amino acid or the ester. b) M. Miyoshi, Bull. Chem. Soc. Jpn., 1973, 46, 1489. c) K. Takeda, Dissertation, University of Tokyo, 1980. d) R. W. Young, K. H. Wood, R. J. Joyce and G. W. Anderson, J. Am. Chem. Soc., 1956, 78, 2126. e) Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.64; H, 7.69; N, 7.69. Found: C, 62.64; H, 7.75; N, 7.71. f) PMR δ 1.26 (t, J=7.2 Hz, 3H), 1.45 (s, 9H), 2.1 (m, 4H), 3.45 (t, J=6.0 Hz, 2H), 3.97 (d, J=5.5 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 4.25 (m, 1H), 7.15 (br.s, NH).

hindered pivalic acid to the N-benzyl-N-methyl tertiary amide (**9**) (93%) and of free-hydroxyl stearic acid to the amide (**10**) (86%). Chemoselective N-acylations of p-hydroxyphenethylamine (tyramine), 5-hydroxypentylamine and 2-mercaptoethylamine could be performed by DPPOx-acetic (or benzoic) acid in 94%, 85% and 80% yields, respectively.

A direct esterification by this reagent may be feasible only in the presence of cesium fluoride as provided by a typical example of benzyl acetate (64% yield), but this method has only limited use, due to side reactions of O-phosphorylation and facile cleavage of phenyl-phosphate bonds.

Preparation of 3-acyl-2-oxazolones

The phosphonate (**5**) undergoes the smooth conversion of a wide variety of carboxylic acids into the corresponding oxazoloides (**6**) under mild neutralizing con-

ditions. Thus, treatment of carboxylic acids with slight excess of the reagent (1.2 equiv) in acetonitrile at room temperature or under cooling gave generally excellent yields of the 3-acyl-oxazolides (**6**), as indicated in Table 3. Most of the oxazolides are fairly stable crystalline compounds, rather unreactive to OH functions, and hence easily handled. The CO absorptions at about 1720 cm^{-1} in the IR spectra reflect higher reactivity of the oxazolides (**6**) toward nucleophilic reagents than that of 3-acyl-2-oxazolidinones (**2**) which show the bands below 1700 cm^{-1}.

This particular process was mild and selective enough to effect the successful conversions to the oxazolides **6** of free-hydroxy carboxylic acids with OH group unaffected and of optically active N-alkoxycarbonyl α-amino acids with practically no racemization judged from the optical activity of the derived di-peptides. Very labile 3-formyl-oxazolide (**6a**), which might not be otherwise easily accessible, was similarly obtained.

Highly sterically hindered carboxylic acid, 2,4,6-trimethylbenzoic acid did not afford the oxazolide, but a quantitative yield of the anhydride (**11**) on the similar treatment at room temperature.[16] Even prolonged heating at 80° gave a poor yield of the oxazolide (**12**) in addition to **11**. Thus, the anhydrides should be taken into account as plausible intermediates besides the phosphorus compounds anticipated for the oxazolide formation (Chart 2).

N-Cbz-L-serine failed to give such an active amide, presumably due to a facile dehydration. This is substantiated by a quite ready conversion of the methyl ester (**13**) to dehydro-alanine (**14**) on treatment with DPPOx at room temperature, providing a feasible route to the dehydro peptides of biological interests.[17]

$$\underset{\text{OH}\quad\text{NH-Cbz}}{\overset{|\quad|}{\text{CH}_2\text{-CH-COOCH}_3}} \xrightarrow[95\%]{\text{DPPOx}} \underset{\text{NH-Cbz}}{\overset{|}{\text{CH}_2\text{=C-COOCH}_3}}$$

13 **14**

Reactivities of 3-acyl-2-oxazolones

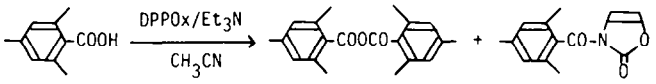
Table 4 indicates chemo- and regioselective features in the acylations of amino, hydroxyl and thiol groups by the 3-acyl-oxazolides (**6**), which have an advantage of easy removal of the resulting deacylated heterocycles due to a high water-solubility. Amino functions are much superior nucleophiles to the latter two groups which must be activated by the appropriate catalysts for smooth acylation.

(a) *Amide formation.* The oxazolides completed the acylation of primary aliphatic amines on mere mixing in aprotic solvents at room temperature within a few minutes. Such a facile aminolysis under mild conditions offers a promising route to peptide synthesis as well as amino protections. Thus, N-alkoxycarbonyl α-amino acid oxazolides serve well as active reagents for peptide coupling with no virtual racemization (Table 2, route-**b**). In this way, free glycine was coupled in aqueous acetonitrile to give high yield of free carboxyl dipeptide.

Chemoselective acylation of spermidine (**15**) could be performed by treatment with 3-*trans* cinnamoyl-2-oxazolone (**6c**) to give a 76% yield of maytenine (**16**), a bioactive alkaloid,[18] without a prectection of secondary amino function. This is presumably due to selective protection by the intramolecular H-bonding, as previously pointed out.[3c]

$$\underset{\textbf{15}}{\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}_2} \xrightarrow[\text{CH}_3\text{CN}]{\textbf{6c}} \underset{\textbf{16}}{\text{PhCH=CHCONH}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NHCOCH=CHPh}}$$

Reaction rates among the amines were shown to decrease in a general order, comparable to that obtained by 3-acyl-2-thiazolidinethiones,[19] *viz.* aliphatic amines ≫ aromatic amines; $RCH_2NH_2 < RR'CHNH_2 >$



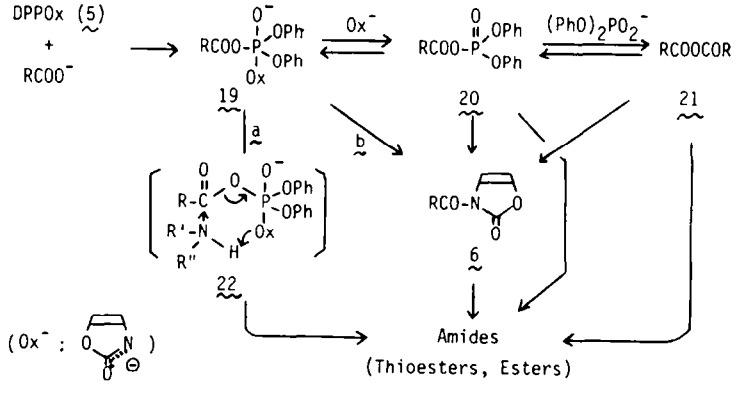


Chart 2.

Table 3. Yields and physical data of 3-acyl-2-oxazolones (6) prepared by DPPOx (5)[a]

Oxazolide : Acyl Group	Yield (%)	mp (°)	IR (Nujol) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$) (δ)	Analysis Calcd [Found]
6a : HCO	46	28	1790 1707	6.93(d,J=2.0Hz,1H), 7.18(d,J=2.0Hz,1H) 8.92(s,1H)	MS calcd for M^+: m/z 113.0111, found: m/z 113.0106.
6b : PhCO	95	85	1805 1699	6.44(d,J=2.0Hz,1H), 7.22(d,J=2.0Hz,1H) 7.35-7.85(m, 5H)	(lit.[11])
6c : PhCH=CHCO	96	109	1770 1690	6.85(d,J=2.0Hz,1H), 7.33(d,J=2.0Hz,1H) 7.2-7.7(m, 5H), 7.94(s, 2H)	C, 66.98 [67.02]; H, 4.19 [4.22] N, 6.51 [6.26]
6d : Ph_2CHCO	94	116	1780 1725	6.43(s, 1H), 6.62(d,J=2.3Hz,1H) 7.18(d,J=2.3Hz,1H), 7.23(s, 10H)	C, 73.11 [72.97; H, 4.69 [4.65 N, 5.02 [4.81]
6e : $CO(CH_2)_4CO$	98	125	1790 1730	1.62-1.92(m, 4H), 2.88-3.16(m, 4H) 6.82(d,J=2.4Hz,1H), 7.23(d,J=2.4Hz,1H)	C, 51.43 [51.32; H, 4.29 [4.27] N, 10.00 [9.97]
6f : $HO(CH_2)_{11}CO$	84	81	1770 1733	1.30(m, 18H), 3.00(t,J=6.0Hz,2H) 3.58(t, J=6.0Hz,2H), 6.83(d,J=2.0Hz,1H) 7.24(d,J=2.0Hz,1H)	C, 63.60 [63.48]; H, 8.83 [8.98] N, 4.95 [4.91]
6g : $CH_3(CH_2)_5$OHCH-$(CH_2)_{10}CO$	88	78	1795 1730	0.90(t,J=5.5Hz,3H), 1.28(m, 28H) 3.00(t.J=7.0Hz,2H), 3.60(m, 1H) 6.83(d,J=2.0Hz,1H), 7.25(d,J=2.0Hz,1H)	C, 68.66 [68.38]; H, 10.08 [10.41] N, 3.81 [3.91]
6h : N-Cbz-L-Ala	95	143[c]	1785 1729	1.50(d,J=7.0Hz,3H), 5.09(s, 2H) 5.35(m, 2H), 6.80(d,J=2.0Hz,1H) 7.20(d,J=2.0Hz,1H), 7.30(s, 5H)	C, 57.93 [57.64]; H, 4.83 [4.96] N, 9.66 [9.87]
6i : N-Cbz-Gly	93	120	1790 1730	4.55(d,J=6.0Hz,2H), 5.10(s, 2H) 5.48(m, 1H), 6.82(d,J=2.0Hz,1H) 7.18(d,J=2.0Hz,1H), 7.30(s, 5H)	C, 56.52 [56.22]; H, 4.35 [4.37] N, 10.14 [9.96]
6j : N-Cbz-L-Phe	79	134[d]	1785 1730	2.80(d.d,J=14.0Hz,J'=9.0Hz,1H) 3.18(d.d,J=14.0Hz, J'=5.0Hz,1H) 4.99(s, 2H), 5.70(m, 1H) 6.80(d,J=2.0Hz,1H), 7.15(d,J=2.0Hz,1H) 7.19(s, 5H), 7.23(s, 5H)	C, 65.57 [65.30]; H, 4.92 [4.99] N, 7.65 [7.49]
6k : N-Boc-L-Pro	89	oil[e]	1787 1736	1.37(s, 9H), 1.94(m, 3H), 2.40(m, 1H)[f] 3.50(m, 1H), 5.35(d.d,J=4.0Hz,J'=8.0Hz,1H) 6.80(d,J=2.0Hz,1H), 7.17(d,J=2.0Hz,1H)	

a) For reaction conditions, see the text. b) The carbonyl absorptions are attributable to oxazolone rings and acyl groups, respectively. c) $[\alpha]_D$ +11.1° (acetone). d) $[\alpha]_D$ +43.6°(acetone). e) $[\alpha]_D$ -54.0° (acetone). f) Determined at 68°C. The ^1H NMR specrum, when measured at 22°C, showed an unequivalence of tert. butyl protons due to the rotamers, which were undistinguishable at 68°C.

Table 4. Acylation of nucleophiles by 3-acyl-2-oxazolones (**6**)[a]

Nucleophile	Acylating Reagent	Time (h)	Solvent	Yield (%)
a: Amines				
$PhCH_2NH_2$	1	0.1	Benzene	91
$PhCH_2NHCH_3$	1	3.5	CH_3CN	88
$PhNH_2$	1	4	THF	91
1-Adamantane-methylamine	1	6	CH_3CN	85
1-Adamantamine	1	6	CH_3CN	41
$HO(CH_2)_5NH_2$	1	0.5	THF	97[b]
p-HO-$PhCH_2CH_2NH_2$	1	0.5	THF	98[b]
o-Aminophenol	1	6	DMF	97[b]
$HSCH_2CH_2NH_2$	1	0.5	CH_3CN	75[b]
b: Thiols				
$PhCH_2SH$	1	74	DMF	0
	1 + Et_3N[c]	0.5	DMF	93
n-BuSH	6d + Et_3N[c]	2	CH_3CN	95
t-BuSH	6d + Et_3N[c]	20	CH_3CN	63
$HOCH_2CH_2SH$	6b + Et_3N[c]	1	CH_3CN	63[d](18)[e]
c: Alcohols				
$PhCH_2OH$	1	20	CH_3CN	0
	1 + CsF[f]	1	CH_3CN	90
1,4-Nonanediol	1 + CsF[f]	18	CH_3CN	83[g](5)[h]
$PhCH(OH)CH_2OH$	1 + CsF[f]	1	CH_3CN	42[g](14,[i] 26[h])
d: Active Methylenes				
CH_3NO_2	6b + DBU	1 (0°)	DMF	59
$CH_2(CN)_2$	6b + DBU	0.3 (0°)	THF	87
$CH_2(CN)COOC_2H_5$	6b + DBU	0.3 (0°)	THF	96

a) The reactions were conducted using slight excess of the oxazolides (1.2 equiv) at room temperature. b) N-Acylated product. c) Two equimolar amounts were used. d) S-Acetate (Thioester). e) S,O-Diacetate. f) Used in excess (3 equiv). g) Primary alkyl ester. h) Diacetate. i) Secondary alkyl ester.

$RR'R''CNH_2$; primary amines > secondary amines. The acyloxazolides also underwent a highly chemoselective amino protection of amino alcohols, amino phenols and amino thiols as shown in Table 4.

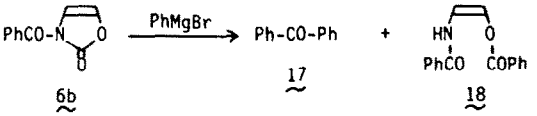
(b) *Thiol ester formation.* Thiols reacted smoothly with the oxazolides to give the thiol esters in the presence of triethylamine at room temperature, though they were completely unreactive in the absence of base. The yield was still moderately high even in the reaction of sterically hindered diphenylacetyl derivative (**6d**) with tertiary thiol. Preferential S-acylation of 2-mercapto-ethanol to the hydroxy thiol ester was readily performed by the same procedure.

(c) *Ester formation.* The oxazolides are generally unreactive toward alcohols in the absence of the catalysts such as Lewis acids, tertiary amines and fluoride ions. The use of cesium fluoride[20] resulted in a great enhancement of the reactivities of OH groups under neutral conditions. This particular process permits a regioselective protection of 1,4-nonanediol to yield the primary alkyl ester preferentially. The selectivity was not so high in the 1,2-diol system such as phenylethyleneglycol which could readily undergo a fluoride-catalyzed acyl migration, presumably via ortho carbonate intermediates.

(d) *C-acylation.* Benzoyloxazolide (**6b**) smoothly acylated the active methyl and methylene compounds such as nitromethane and malonic acid derivatives in the presence of 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) (at 0°) or triethylamine (at room temp). Thus, the corresponding phenyl ketones were formed in good yields within 1 hr (Table 4d).

Reaction of **6b** with Grignard reagent (PhMgBr) gave benzophenone (50%) in addition to the ring-cleaved product, *cis* 2-(benzamido)vinyl benzoate (**18**) (34%), whose isolation was in contrast to the previous observations on exclusive formation of N-acylamino ketones.[21]

(e) *Reduction to alcohols and aldehydes.* The borohydride reduction of the oxazolides under ice-cooling



6b 17 18

gave high yields of the alcohols within 10 min. Partial reduction of the 3-acyl moieties to aldehydes by lithium tri-t-butoxyaluminohydride or diisobutylaluminium hydride in tetrahydrofuran was not so satisfactory as that of 3-acyl-2-thiazolidinethiones.[3] The yield of benzaldehyde from **6b** did not go up to over 60% in repeated attempts.

Plausible mechanism (*Chart* 2)

Among several plausible pathways involved in the carboxyl activating processes described here, the pathes *a* and *b* via the pentacovalent phosphorus intermediates (**19**) initially formed would be generally more important than the alternatives which might accompany appreciable racemizations, since α-amino acid oxazolides (**6h,j,k**) and the model tripeptide (**8**) could be formed in good optical activity. Thus, direct formation of amides (and esters) may involve the coupling in a concerted manner like **22**, though other intermediates (**20** and **21**) anticipated here would be cooperative to a lesser extent.

The synthetic versatility of 2-oxazolone moiety as a good leaving group is obvious as demonstrated here by rather limited numbers of the examples and may be readily extended to further applications such as the intramolecular cyclizations to lactams and lactones, and the activations of silyl, sulfur and selenium compounds.

EXPERIMENTAL

M. ps were determined on a Yanaco hot stage apparatus and are uncorrected. The 100 MHz and 60 MHz ^{1}H NMR spectra were recorded on JEOL JNM-FX-100 and Hitachi R-24B spectrometers, respectively, in $CDCl_3$ with 1% TMS. High resolution mass spectra were determined with a JEOL JMS-D-300 spectrometer equipped with a JMA-2000 data analyzer and with a direct-inlet system. Optical rotations were taken on a JASCO DIP-140 polarimeter using a 0.5 dm cell.

Diphenyl 2-oxo-3-oxazolynylphosphonate (*3-diphenoxyphosphoryloxazol-2-one*) [*DPPOx*] (**5**). Et_3N (5.42 g, 53.7 mmol) was dropwise added to an ice-cooled soln of 2-oxazolone[11] (4.52 g, 53 mmol) and diphenyl chlorophosphate (14.02 g, 52 mmol) in MeCN or CH_2Cl_2 (50 mL). The mixture was stirred at 0° for 1 hr and then kept at room temp overnight. The resulting ppts were filtered off and washed with CH_2Cl_2. The combined filtrate and washings were evaporated *in vacuo* below 30° to leave an oil which was chromatographed on silica gel to give the DPPOx as a colorless solid, 15.8 g (96%), m.p. 51° (from n-hexane), b.p. 150–60°/0.03 mmHg (bath temp at 200°), IR(KBr) 1788, 1300 cm^{-1}, ^{1}H NMR δ 6.74 (d,d, J = 2.4 Hz, J′ = 2.5 Hz, 1H), 6.81 (d,d, J = 1.7 Hz, J′ = 2.4 Hz, 1H), 7.32 (b.s, 10H), MS calc for M^+ m/z 317.0452, found *m/z* 317.0429. (Found: C, 56.84; H, 3.89; N 4.29. Calc for $C_{15}H_{12}NO_5P$: C, 56.79; H, 3.81; N, 4.41%).

Though this reagent was stable in a prolonged storage with protection against moisture, treatment with a 50% aqueous THF at room temp resulted in a gradual hydrolysis to 2-oxazolone and diphenyl phosphate over a period of 20 hr.

Methyl diphenyl phosphate (**7**, XR′ = OMe)

(a) A soln of the DPPOx (0.16 g, 0.5 mmol) in MeOH (1 mL) was stirred in the presence of catalytic amounts of CsF for 5 min. The solvent was removed *in vacuo* below 20° and the resulting product was purified by chromatography on silica gel twice to give a colorless oil, 0.13 g (97%), ^{1}H NMR δ 3.87 (d, J = 11.0 Hz, 3H), 7.19 (s, 10H). MS calc for $C_{13}H_{13}O_4P$ (M^+): *m/z* 264.0549, found: *m/z* 264.0519.

(b) *Without the catalyst*, the same treatment as above gave a mixture of unchanged **5** and **7** (XR′ = OMe) in nearly equal amounts even after stirring for 20 hr.

Diphenyl benzylphosphoramidate (**7**) (XR′ = $NHCH_2C_6H_5$)

The DPPOx (0.16 g, 0.5 mmol) was treated with benzylamine (0.05 g, 0.46 mmol) in MeCN (2 mL) at room temp for a week. Preparative layer chromatography (CH_2Cl_2) gave the phosphoramidate as colorless crystals, m.p. 100–103° (from n-hexane) (lit.[22] m.p. 103–104°), 80 mg (51%), ^{1}H NMR (in addition of D_2O) δ 4.24 (d, J = 11.0 Hz, 2H), 7.27 (s, 15H).

Direct acylation of amines

General procedure. The DPPOx (1.2 equiv) was added to the equimolar solns of a carboxylic acid, a primary or secondary amine and Et_3N in MeCN or DMF and the mixture was stirred at room temp for 0.5–20 hr. After removal of the solvent, the residue was taken up in organic solvent such as EtOAc, and washed successively with HCl aq and $NaHCO_3$ aq. Evaporation of the dried organic soln gave the amide which was further purified by chromatography on silica gel or recrystallization. Typical examples for direct preparation of amides by DPPOx method are given below.

N-(3-Phenylpropyl)formamide. A soln of 3-phenylpropylamine (0.14 g, 1 mmol) and formic acid (56 mg, 1.5 mmol) in MeCN (8 mL) was treated with DPPOx (0.35 g, 1.1 mmol) in the addition of Et_3N (0.11 g, 1.1 mmol) for 2 hr to give the formamide as an oil, after purification by chromatography, 0.15 g (89%), IR 1620 cm^{-1}, ^{1}H NMR δ 1.89 (m, 2H), 2.66 (t, J = 6.5 Hz, 2H), 3.28 (*q*, J = 6.5 Hz, 2H), 6.3 (b.s., NH), 7.14 (s, 5H, 8.07 (s, 1H), MS calc for $C_{10}H_{13}NO$ (M^+) *m/z* 163.0997, found *m/z* 163.1003.

N-Benzyl-N-methylpivalamide (**9**). Similar treatment of pivalic acid (0.2 g, 2 mmol) with DPPOx (0.66 g, 2.1 mmol) and N-methylbenzylamine (0.25 g, 2 mmol) gave the tertiary amide, 0.39 g (93%), m.p. 47–49°, IR 1625 cm^{-1}, ^{1}H NMR δ 1.31 (s, 9H), 2.95 (s, 3H), 4.61 (s, 2H), 7.23 (s, 5H), MS calc for $C_{13}H_{19}NO$ (M^+) *m/z* 205.1466, found *m/z* 205.1473.

N-Benzyl-12-hydroxyoctadecanamide (**10**). A soln of 12-hydroxystearic acid (0.3 g, 1 mmol) and benzylamine (0.12 g, 1.1 mmol) in DMF (5 mL) was treated with DPPOx (0.35 g, 1.2 mmol) and Et_3N (0.11 g, 1.1 mmol) for 0.5 hr. Colorless ppts were collected and recrystallized from CH_2Cl_2 to give **10**, 0.33 g (86%), m.p. 101–103°, IR(KBr) 3280, 1634 cm^{-1}, ^{1}H NMR δ 0.90 (uneven t, J = 5.0 Hz, 3H), 1.30 (m, 28H), 2.24 (t, J = 7.0 Hz, 2H), 3.60 (m, 1H), 4.45 (d, J = 5.5 Hz, 2H), 5.90 (NH), 7.31 (s, 5H). (Found: C, 77.42; H, 11.34; N, 3.74. Calc for $C_{25}H_{43}NO_2$: C, 77.12; H, 11.05; N, 3.60%).

Preparation of peptides

N-Benzyloxycarbonyl-L-alanylglycine ethyl ester. A mixture of DPPOx (0.39 g, 1.2 mmol), N-Cbz-L-alanine (0.23 g, 1.0 mmol) and glycine ethyl ester hydrochloride (0.14 g, 1.0 mmol) in MeCN (6 mL) was stirred in addition of Et_3N (0.22 g, 2 mmol) at room temp overnight. Removal of the solvent followed by usual work-up gave the dipeptide, 0.28 g, (88%), m.p. 97–99°, $[\alpha]_D^{20}$ – 22.0° (*c* = 1, EtOH) (lit.[23] – 22.0°). (Found: C, 58.47; H, 6.40; N, 8.89. Calc for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.49; N, 9.09%).

In this way, N-Cbz-L-Phe-Gly-OEt and N-Boc-L-Phe-L-Ala-OEt were obtained (Table 2, route **a**).

N-Benzyloxycarbonylglycyl-L-alanyl-L-phenylalanine methyl ester (**8**). DPPOx (0.21 g, 0.66 mmol) was added to a cooled soln of N-Cbz-glycyl-L-alanine (0.19 g, 0.66 mmol) and L-phenylalanine methyl ester (0.11 g, 0.6 mmol) in MeCN (1 mL). The mixture was stirred at 0° for 5 hr, then at room temp overnight. Removal of the solvent followed by usual work-up for purification gave a crude **8** (0.26 g, 96%), of which diastereomer ratio [(D-L)/(L-L)] was determined to be 3:97 by high performance liquid chromatography (HPLC) under the following conditions: column, Partisil 5 ODS-3; eluent, MeOH–H_2O (49:51); flow rate, 1.7 mL/min; detection at 254 nm.

The authentic tripeptides, (L-L)-**8** and (D-L)-**8**, prepared by the lit method[15] gave the retention times at 23.5 min and 26.3 min, respectively, under the above HPLC conditions and used as internal standard for the racemization test.

Chemoselective amino protection. Difunctional model compounds, *p*-(2-aminoethyl)phenol (tyramine), 5-hydroxypentylamine and 2-mercaptoethylamine were treated with DPPOx (1.1 equiv), acetic (or benzoic) acid (1.1 equiv) in the addition of Et_3N (1.0 equiv) in MeCN (or DMF) at room temp for 0.5–1.0 hr. Thus, N-(*p*-hydroxyphenylethyl)acetamide (94%), N-(5-

hydroxypentyl)-benzamide (86%) [IR(Film) 3300, 1640 cm^{-1}, ^{1}H NMR δ 1.50 (m, 6H), 2.88 (0H), 3.36 (t, J = 6.0 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 6.85 (NH), 7.4–7.8 (m, 5H), MS calcd for $C_{12}H_{17}NO_2(M^+)$ *m/z* 207.1257, found *m/z* 207.1256] and N-(2-mercapto-ethyl)acetamide (83%) were obtained with negligible amounts of N,O- or N,S-diacylated products.

In the case of aliphatic amino alcohol, the phosphorylation product, tentatively assigned as diphenyl (5-benzamidopentyl) phosphate, was isolated in 5% yield as a major side product, IR(Film) 1638, 1282 cm^{-1}, ^{1}H NMR δ 1.2–1.9 (m, 6H), 3.40 (t, J = 6.0 Hz, 2H), 4.20 (t, J = 6.0 Hz, 2H), 7.13 (s, 10H), 7.2–7.8 (m, 5H), MS *m/z* 439 (M^-), 334, 250, 189.

Benzyl acetate. This provides a typical procedure for a direct esterification of carboxylic acids by DPPOx. To a soln of DPPOx (0.39 g, 1.2 mmol), AcOH (0.06 g, 1 mmol) and Et_3N (0.1 g, 1 mmol) in MeCN (6 mL) were added benzylalcohol (0.09 g, 0.83 mmol) and CsF (0.2 g) which was dried at 140° for 10 hr. The mixture was stirred at room temp overnight. After removal of the insoluble materials, purification of the product by chromatography on silica gel gave the benzyl ester as an oil, 0.08 g (64%) which was identical with the authentic specimen.

3-*Acyl*-2-*oxazolones* (**6**)

General procedure. The DPPOx (1.2 equiv) was added to the equimolar amounts of carboxylic acids and Et_3N in dry Me_3CN under ice-cooling. The mixture was stirred at room temp. for 3–5 hr or overnight. After removal of the solvent *in vacuo* at 20–25°, the resulting oil was chromatographed on silica gel with CH_2Cl_2 as an eluent to give the 3-acyl-oxazolides which were further purified by recrystallization. Some typical examples are given as follows.

3-*Diphenylacetyl*-2-*oxazolone* (**6d**). A soln of diphenylacetic acid (1.0 g, 4.7 mmol), DPPOx (1.6 g, 5.0 mmol) and Et_3N (0.51 g, 5.0 mmol) in dry MeCN (10 mL) was stirred at room temp. for 5 hr to give the oxazolide as colorless crystals, 1.24 g (94%), m.p. 114–116° (from n-hexane).

Adipoyl-3,3'-*di*-2-*oxazolone* (**6e**). A soln of adipic acid (0.15 g, 1.0 mmol) in MeCN (5 mL) was treated with DPPOx (0.77 g, 2.4 mmol) in the presence of Et_3N (0.24 g, 2.4 mmol) at room temp. for 5 hr to give the oxazolide as colorless crystals, 0.28 g (98%), m.p. 124–125°.

3-(12-*Hydroxystearoyl*)-2-*oxazolone* (**6g**). Treatment of 12-hydroxystearic acid (1.0 g, 3.3 mmol) with DPPOx (1.25 g, 3.9 mmol) in the presence of Et_3N (0.4 g, 3.9 mmol) in MeCN (30 mL) gave the oxazolide with OH group unaffected. Recrystallization from n-hexane gave colorless needles, 1.08 g (88%), m.p. 75–78°.

3-(N-*Carbobenzyloxy*-L-*alanyl*)-2-*oxazolone* (**6h**). A soln of N-carbobenzyloxy-L-alanine (0.5 g, 2.2 mmol) and Et_3N (0.23 g, 2.3 mmol) in MeCN (10 mL) was treated with DPPOx (0.85 g, 2.7 mmol) at room temp. overnight. After removal of the solvent below 20°, the product was purified by chromatography to give a colorless solid, 0.62 g (95%), $[\alpha]_D^{20}$ + 11.1° (*c* = 3, acetone), m.p. 140–143° (from n-hexane-CH_2Cl_2).

2,4,6-*Trimethylbenzoic anhydride* (**11**). A mixture of DPPOx (0.32 g, 1.0 mmol) and 2,4,6-trimethylbenzoic acid (0.17 g, 1.0 mmol) in MeCN (5 mL) was stirred in the presence of Et_3N (0.12 g, 1.2 mmol) at room temp. for 1 hr. Removal of the solvent followed by chromatography on silica gel (benzene-n-hexane 2:1) gave the anhydride **11** as colorless crystals, 0.15 g (95%), m.p. 102–105° (lit.[24] 103–104°), IR(Nujol) 1783, 1728 cm^{-1}, ^{1}H NMR δ 2.28 (s, 6H), 2.38 (s, 12H), 6.86 (s, 4H). (Found: C, 76.93; H, 7.23. Calc for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%).

3-(2,4,6-*trimethylbenzoyl*)-2-*oxazolone* (**12**). A soln of DPPOx (0.33 g, 1.03 mmol), 2,4,6-trimethylbenzoic acid (0.17 g, 1.03 mmol) and Et_3N (0.13 g, 1.3 mmol) in MeCN (10 mL) was refluxed for 10 hr to give the oxazolide as colorless crystals, 0.04 g (17%), m.p. 106–108° (from n-hexane) in addition to **11**(0.125 g, 78%). IR(Nujol) 1783, 1710 cm^{-1}, ^{1}H NMR δ 2.20 (s, 6H). 2.31 (s, 3H), 6.82 (d, J = 2.0 Hz, 1H), 6.88 (s, 2H), 7.26 (d, J = 2.0 Hz, 1H). (Found: C, 67.32; H, 5.67; N, 5.91. Calc for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06%).

Methyl 2-(*benzyloxycarbonylamino*)*acrylate* (**14**). A soln of **13** (0.13 g, 0.5 mmol) in MeCN (5 mL) was treated with DPPOx (0.2 g, 0.63 mmol) in the presence of Et_3N (0.08 g, 0.79 mmol) at room temp. overnight to give the dehydrated product as a colorless oil, 0.115 g (95%), IR(Film) 3400, 1740, 1720, 1640 cm^{-1}, ^{1}H NMR δ 3.68 (s, 3H), 5.02 (s, 2H), 5.66 (d, J = 1.0 Hz, 1H), 6.11 (s, 1H), 7.15 (s, 5H). MS calc for $C_{12}H_{13}NO_2$ (M^+) *m/z* 235.0845, found *m/z* 235.0850.

Amide formation

General procedure. A mixture of **1** (1.2 equiv) and an amine in aprotic solvents such as MeCN, THF and benzene was stirred at room temp. or under cooling for 10 min to 10 hr. After dilution with CH_2Cl_2 or AcOEt, the mixture was successively washed with 10% HCl aq and water. Removal of the solvent gave an amide which was further purified by recrystallization or chromatography on silica gel. The isolated yields are given in Table 4.

The following acetamides were characterized by the mps and spectral (IR and ^{1}H NMR) data which were identical with those of the authentic samples: N-benzyl (m.p. 60°), N-phenyl (m.p. 110°), N-benzyl-N-methyl (m.p. 41°), N-1-adamantyl (m.p. 146°), N-(*p*-hydroxyphenetyl) (m.p. 132°) and N-(o-hydroxyphenyl)-acetamines (m.p. 129°).

N-(5-*Hydroxypentyl*)*acetamid.* Oil, IR(neat) 3300, 1640 cm^{-1}, ^{1}H NMR δ 1.1–1.8 (m, 6H), 1.98 (s, 3H), 3.19 (q, J = 6.0 Hz, 2H), 3.59 (t, J = 6.0 Hz, 2H), 3.80 (s, 1H), 6.80 (b.s, 1H), MS calcd for $C_7H_{15}NO_2$ (M^+), *m/z* 145.1102; found *m/z* 145.1127.

N-(2-*Mercaptoethyl*)*acetamide.* Oil, IR(neat) 1620 cm^{-1}, ^{1}H NMR δ 1.40 (t, J = 7.0 Hz, 1H), 1.94 (s, 3H), 2.45–3.10 (m, 2H), 3.35 (q, J = 7.0 Hz, 2H), 6.60 (b.s, 1H). MS calc for C_4H_9NOS (M^+), *m/z* 119.0405, found *m/z* 119.0415.

Dipeptides. In a similar way as above, fully protected dipeptides were obtained as shown in Table 2 (route **b**). Free carboxy peptide, N-Cbz-L-phenyl-alanylglycine was obtained by treatment of N-protected **6j** (0.19 g, 0.51 mmol) with the soln of glycine (0.04 g, 0.55 mmol) and Et_3N (0.053 g, 0.52 mmol) in aqueous MeCN (5 mL) at room temp. (overnight).

Maytenine (N,N'-*di*-trans-*cinnamoylspermidine*) (**16**). To a soln of **15** (0.15 g, 1.0 mmol) in MeCN (15 mL) was added 3-*trans* cinamoyl-2-oxazolone (0.45 g, 2.1 mmol) at room temp. In a few min, the ppt started to be deposited. After stirring for 1 hr the ppt was collected and recrystallized from acetone to give maytenine, 0.31 g (76%), m.p. 154–156° (lit.[18] 158°), IR (Nujol) 3300, 1648, 1610, 1540 cm^{-1}. (Found: C, 73.93; H, 7.85; N, 10.37. Calc for $C_{15}H_{20}N_2O_5$: C, 74.07; H, 7.65; N, 10.37%).

Thiol ester formation

General procedure. A soln of **6** (1.2 equiv) and a thiol in MeCN or DMF was stirred in the presence of Et_3N (2 equiv) at room temp. Removal of the solvent followed by chromatography on silica gel gave the thioester. As indicated in Table 4(b), no thioester was formed in the lack of Et_3N.

S-*Benzyl thioacetate.* Colorless oil, IR(neat) 1685 cm^{-1}, ^{1}H NMR δ 2.24 (s, 3H), 4.07 (s, 2H), 7.22 (s, 5H). The spectral data were identical with those of the authentic specimen.

S-*n*-*Butyl diphenylthioacetate.* Oil, IR(neat) 1680 cm^{-1}, ^{1}H NMR δ 0.85 (uneven t, J = 6.5 Hz, 3H), 1.45 (m, 4H), 2.85 (t, J = 7.0 Hz, 2H), 5.16 (s, 1H), 7.23 (s, 10H), MS calc for $C_{18}H_{20}OS$ (M^-), *m/z* 284.1233, found *m/z* 284.1236.

S-*t*-*Butyl diphenylthioacetate.* M.p. 82–85° (from n-hexane), IR (Nujol) 1670 cm^{-1}, ^{1}H NMR δ 1.42 (s, 9H), 5.10 (s, 1H), 7.25 (s, 10H). (Found: C, 75.76; H, 7.03. Calc for $C_{18}H_{20}OS$: C, 76.06; H, 7.04%.)

S-2-*Hydroxyethyl thiobenzoate.* Oil, IR(neat) 1660 cm^{-1}, ^{1}H NMR δ 2.95 (b.s, OH), 3.22 (t, J = 6.0 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H), 7.05–7.50 (m, 3H), 7.65–8.00 (m, 2H). In addition to the above monobenzoate, the S,O-dibenzoate [IR(neat) 1720 and 1663 cm^{-1}] was isolated in 18% yield.

Ester formation

General procedure. To a soln of **1** (1.2 equiv) and an alcohol in MeCN was added excess CsF (2–3 equiv) as activator which was dried at 150° under vacuum. The mixture was stirred at room temp. generally for 1 hr. After removal of the insoluble materials, usual work-up followed by chromatography on silica gel gave the

ester. In the place of CsF, anhyd $AlCl_3$ and Et_3N were also usable as the efficient catalysts for such a conversion.

Benzyl acetate. This was identical with the authentic compound with regard to the spectral data.

1,4-*Nonanediol* 1-*monoacetate.* Colorless oil, IR(neat) 3400, 1740 cm^{-1}, ^1H NMR δ 0.92 (t, J = 5.0 Hz, 3H), 1.1–1.9 (m, 12H), 1.92 (s, 3H), 2.15 (s, OH), 3.3–3.8 (m, 1H), 4.08 (t, J = 6.0 Hz, 2H). The parent peak (M^+) was not detected in the MS spectrum.

1-*Phenyl*-1,2-*ethanediol,* 2-*monoacetate.* IR(Neat) 3450, 1725 cm^{-1}, ^1H NMR δ 1.99 (s, 3H), 3.30 (d, J = 3.5 Hz, OH), 4.1–4.3 (m, 2H), 4.87 (q, J = 4.0 Hz, 1H), 7.27 (s, 5H). In addition, the 1-*monoacetate* [^1H NMR δ 2.05 (s, 3H), 2.7 (b.s, OH), 3.77 (b.t, J = 6.0 Hz, 2H), 5.80 (t, J = 6.0 Hz, 1H), 7.29 (s, 5H)] and the 1,2-*diacetate* [^1H NMR δ 2.01 (s, 3H), 2.08 (s, 3H), 4.31 (d, J = 6.0 Hz, 2H), 6.01 (t, J = 6.0 Hz, 1H), 7.29 (s, 5H)] were also isolated by chromatography on silica gel.

2-*Nitroacetophenone.* **6b** (0.19 g, 1 mmol) was added to a soln of nitromethane (0.06 g, 1 mmol) and DBU (0.32 g, 2 mmol) in DMF (5 mL) at 0° and the mixture was kept for 1 hr to give the C-acylation product, 0.095 g (59%), m.p. 107–108° (lit.[25] 106–108°), IR (KBr) 1690, 1550, 1330 cm^{-1}, ^1H NMR δ 5.85 (s, 2H), 7.25–7.95 (m, 5H).

Benzoylmalononitrile. A soln of malononitrile (0.08 g, 1 mmol) and **6b** (0.22 g, 1.2 mmol) in THF (10 mL) was kept at 0° in the presence of DBU (0.3 g, 2 mmol) for 20 min to give the phenyl ketone, 0.16 g (87%), m.p. 122° (lit.[25] 129°), IR (KBr) 3400, 2220, 1605 cm^{-1}. The use of Et_3N in the place of DBU was also satisfactory.

Ethyl cyanobenzoylacetate[25] was similarly obtained in 96% yield.

cis 2-(*Benzamido*)*vinyl benzoate* (**18**). To a cooled soln of **6b** (0.19 g, 1 mmol) in THF (5 mL) was added a 2M soln of PhMgBr in THF (0.6 mL) and the mixture was kept at 0° for 4 hr. Usual work-up followed by chromatography on silica gel gave benzophenone (0.09 g, 50%) in addition to the ring-cleaved **18** (0.09 g, 34%), m.p. 174–175° (from CH_2Cl_2-n-hexane), IR (KBr) 1730, 1643 cm^{-1}, ^1H NMR δ 6.75 (t, J = 5.4 Hz, 1H), 7.05 (t, J = 5.4 Hz, 1H), 7.28–7.75 (m, 7H), 7.75–8.0 (m, 2H), 8.0–8.35 (m, 2H). (Found: C, 72.04; H, 4.96; N, 5.25. Calc for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24%.)

Reduction to alcohols

2,2-*Diphenylethanol.* A soln of **6d** (0.3 g, 1 mmol) in THF (10 mL) was treated with $NaBH_4$ (0.1 g, 2.6 mmol) at room temp. for 10 min. After usual work-up, the product was purified by recrystallization from n-hexane to give the alcohol as colorless needles, m.p. 50–51° 0.19 g (89%), ^1H NMR δ 1.71 (s, OH), 4.07 (s, 3H), 7.17 (s, 10H). (Found: C, 54.90; H, 7.17. Calc for $C_{14}H_{14}O$: C, 54.84; H, 7.07%.)

In a similar manner, *benzylalcohol* was obtained in 89% yield from **6b**.

Benzaldehyde from 3-*benzoyl*-2-*oxazolone* (**6b**). **6b** (0.19 g, 1 mmol) was added to a THF (5 mL) soln of lithium tri-t-butoxyaluminium hydride (0.3 g, 1.2 mmol) at −40° and the mixture was stirred at −10° for 1–2 hr. After decomposition with dilute H_2SO_4 soln, the product was separated by preparative TLC on silica gel to give benzaldehyde (0.06 g, 60%), which was identified by direct comparison with the authentic sample.

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