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A NEW REAGENT FOR ACTIVATING CARBOXYL GROUPS: DIPHENYL 2-OXO-3-OXAZOLINYLPHOSPHONATE

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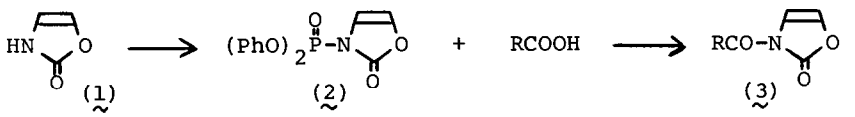
[Summary] Diphenyl 2-oxo-3-oxazolinylphosphonate serves as a carboxyl-activating reagent to permit a direct preparation of versatile intermediate, 3-acyl-2-oxazolones or a one-step formation of amides from carboxylic acids.

Activation of carboxyl groups under mild conditions is apparently of great value as a fundamental process in a wide scope of organic synthesis. In connection with synthetic study on the 2-oxazolone telomers[1], 2-oxazolone moiety, in contrast with 2-oxazolidinone, has proved of much potential as an excellent leaving group in carboxyl-activating process. Thus, 3-acyl- and 3-alkoxycarbonyl-2-oxazolones were recently introduced as a "ready-to-use" type of reagents for amino-protection[2].

This paper describes the preparation and applications of diphenyl 2-oxo-3-oxazolinylphosphonate (2) [DPPOx] as a new carboxyl-activating reagent, which permits a direct preparation of versatile synthetic intermediate, 3-acyl-2-oxazolones, or a one-step conversion of carboxylic acids into amides or esters.



Treatment of 2-oxazolone (1) in equimolar amounts with diphenyl phosphorochloridate in the presence of base (triethylamine) in methylene chloride at room temperature gave a nearly quantitative yield of the phosphonate (2) as colorless crystals , mp 51° (bp ~160°/0.03mmHg), IR(nujol) 1790, 1755 cm^{-1}, NMR($CDCl_3$) δ6.74 (1H,t,J=2.4Hz)[3], 6.81(1H,d.d,J=2.4Hz,J'=1.6Hz)[3], 7.32(10H,b.s), which could be stored at room temperature for months without any practical decompositions.

This reagent could undergo the smooth conversion of a variety of carboxylic acids including N-protected α-amino acids into the corresponding oxazolides generally in high yields under mild conditions. The reaction was mild and selective enough to afford optically active oxazolides derived from α-amino acids without practical racemization or remain free secondary hydroxy groups unaffected.

Thus, on treatment with the reagent 2 (1.2eq) and triethylamine in acetonitrile at room temperature, N-Cbz-L-alanine and 12-hydroxystearic acid gave 95% and 88% yields of the 3-acyl-oxazolides, respectively, though N-Cbz-L-serine failed to give the oxazolide, presumably due to a facile dehydration. Some representatives are summarized in Table I.

3-Acyl-2-oxazolones (3) thus formed have much synthetic potential due to high reactivity toward a variety of nucleophiles (including hydride and carbanions)[4] and a facile homopolymerization[1] leading to the polymeric reagents[5], particularly in a smooth peptide formation and a selective protection of amino functions.

Table I. 3-Acyl-2-oxazolones derived from 3-Oxazolinylphosphonate 2 and RCOOH[a]

RCOOH	Yield	mp	$[\alpha]_D^{25}$ (acetone)
HCOOH	46%	28°	
PhCOOH	95	85	
$PhCH_2CH_2COOH$	96	36	
12-OH-stearic acid	88	78	
$HOOC(CH_2)_4COOH$	98	125	
N-Cbz-L-Ala	95	143	+11.1° (c 3)
N-Cbz-Gly	93	120	
N-Cbz-L-Phe	79	134	+43.6 (c 2)
N-Boc-L-Pro	77	oil	-49.2 (c 4.9)
N-Cbz-L-Ser	0		

a) The reactions were carried out at room temperature in CH_3CN using the reagent 2 (1.2eq) in the presence of Et_3N (1.2eq).

Facile aminolysis of the oxazolides 3 with amino acids or the esters under mild conditions provides a promising route to peptides and thus, nearly optically pure dipeptides could be obtained (route a in Table II). Highly selective N-acylation with 3-acetyl-2-oxazolone (2eq) (at room temperature) was demonstrated with amino-alcohols and -phenols such as 3-amino-1-propanol (THF, < 1hr, 100%), tyramine (DMF, < 1hr, 98%) and p-aminophenol (THF, ~7hr, 90%). However, in addition of catalytic or stoichiometric amounts of tertiary amines, the Lewis acids or cesium fluoride, the oxazolides 3 underwent smooth acylation of alcohols and thiols at room temperature and thus, 3-acetyl-2-oxazolone (1.2eq) gave benzyl acetate (90%) and 1,5-nonanediol 1-monoacetate (83%) in the presence of cesium fluoride, and benzyl thioacetate (93%) in the presence of triethylamine within 1-2hr.

Table II. Preparation of Dipeptides[a]

	route a[b]	route b[c]	$[\alpha]_D$ (EtOH)
N-Cbz-L-Ala-Gly-OEt	98%	88%	-22.0° (c 1)[d]
N-Cbz-L-Phe-Gly-OH	89		-17.0 (c 1.2)[e]
N-Cbz-L-Phe-Gly-OEt	95	83	-16.8 (c 5)[f]
N-Boc-L-Phe-L-Ala-OEt		90	-14.6 (c 2.5)
N-Boc-L-Pro-Gly-OEt	94		-58.0 (c 7.8)

a) The reactions were carried out at room temperature in CH_3CN overnight. b) Yield from the aminolysis of the oxazolides with amino acid or the esters (1.2eq). c) Yield from the coupling of amino acids and the esters using 2 (1.2eq) in the presence of Et_3N (1.0eq). d) Lit. -22.2° (Bull.Chem.Soc.Jpn., 46, 1489 (1973)). e) Lit. -16.5° (K. Takeda: Dissertation, 1980, University of Tokyo). f) Lit. -16.9° (J.Am.Chem.Soc., 78, 2126 (1956)).

On the other hand, compound 2 serves as a feasible reagent for one-step amide-synthesis and the direct coupling of N-protected amino acids and amino acid esters proceeded smoothly in acetonitrile at room temperature to give the dipeptides without practical racemization as shown in Table II (route b). Further synthetic applications of the reagent 2 to an intramolecular cyclization are now in progress.

References and Notes

1. Y. Abe and T. Kunieda, Tetrahedron Lett., 5007 (1979).
2. T. Kunieda, T. Higuchi, Y. Abe and M. Hirobe, Tetrahedron Lett., 3065 (1980).
3. Signals at δ6.74 and 6.81 are attributable to the olefinic C-5 and C-4 protons, respectively and J values are assignable as $J_{H,H'}$=2.4Hz, $J_{H,P}$=2.4Hz and $J_{H',P}$= 1.6Hz (long range coupling).
4. $LiAlH(O\text{-}t\text{-}Bu)_3$ and RMgX gave moderate yields of aldehydes and ketones.
5. The polymers still retain reactivity high enough to serve well as selective acylating reagents of poly-amines and poly-alcohols. T. Kunieda, T. Higuchi, Y. Abe and M. Hirobe, in preparation.

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