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Reductive Phosphorylation of 1,2-Dithiolanes with Dialkyl Phosphites

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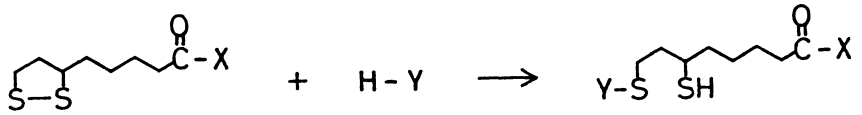
Lipoamide was reductively phosphorylated by dialkyl phosphites in the presence of triethylamine with high regioselectivity. Acid anhydride did not interfere with the phosphorylation. Thus, 6-S-acyldihydrolipoamides bearing 8-S-phosphoryl group were synthesized in one-pot reaction in good yields.

Lipoic acid is known as a cofactor in the enzymatic respiratory reactions of living organisms. One of the working intermediates of the enzyme-bound lipoic acid is in its reduced form, i.e., dihydrolipoic acid derivatives with the 6-mercapto group selectively acylated. Thus, the biological and physiological activity of S-substituted dihydrolipoic acids should be a quite attractive research subject.

A synthetic route to dihydrolipoic acids with the same substituents on the two sulfur atoms is simple, i.e., the substituents are introduced directly to dihydrolipoic acids. On the other hand, a difficulty is encountered when regioselective mono-substitution and asymmetric di-S-substitution on dihydrolipoic acids is intended. The most promising way to this is to use the reductive addition of a component H-Y to the 1,2-dithiolane as depicted in Eq. 1. In line with this strategy, the reductive acylation of lipoic acid with aldehydes has been developed under photochemical and radical conditions.[1] The similar acylation of lipoamide with carboxylic acids and tributylphosphine was also developed by Okawara, et al.[2]



(1)

Various nucleophiles are known to cleave S-S bond of linear dialkyl disulfides. If one uses a nucleophile Y^-, a conjugate base of an acid H-Y in the reaction with lipoyl derivatives, reductive mono-substitution would result in a similar manner to Eq. 1. We wish to report here the reductive phosphorylation of

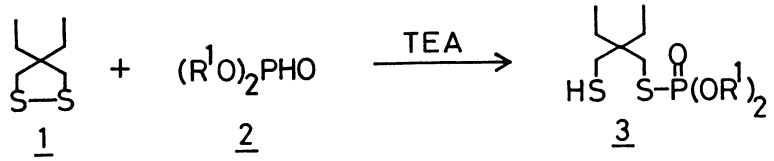
the dithiolanes with dialkyl phosphites. The corresponding reaction of open-chain disulfides has already been reported.[3)]

We started the study by using a simple model of lipoyl derivatives, i.e., 4,4-diethyl-1,2-dithiolane (1), which is resistant to ring-opening polymerization.[4)] Reaction of 1 with dialkyl phosphites 2 in TEA gave mono-S-phosphorylated 1,3-propanedithiols 3 in good yields (Table 1). Sodium salt of the phosphites is required to react with linear disulfides,[3)] but weak base TEA is enough to activate the phosphite to react with 1,2-dithiolane 1. This is probably due to the ring-strain of 1,2-dithiolane.[5)] In fact, BuSSBu virtually did not react under the similar conditions. When dimethyl phosphite was reacted for a longer period or at a higher temperature, a complicated mixture resulted. Intermolecular methyl transfer from phosphorus esters to mercapto group of 3 was suggested from the ^{1}H NMR spectra of the non-acidic products. Similar side-reaction was observed in the reaction of linear disulfides.[3)] The products 3 are relatively unstable, and Kugelrohr-distillation caused serious decomposition.

Table 1. Reactions of 4,4-Diethyl-1,2-dithiolane with Dialkyl Phosphites[a)]

1(mmol)	2,R^1(mmol)	Et_3N(ml)	Time/ min	Yield/%(3)[b)]
3.05	Me,3.70	3.3	20	90(3a)
3.33	Me,3.02	5.0	48h	d)
3.33	Me,3.21	5.0	240[c)]	d)
3.01	Et,3.70	2.5	60	87(3b)
3.03	i-Pr,3.70	2.5	210	89(3c)
3.26	Bu,3.77	2.5	90	97(3d)
0.36	Ph,0.43	0.2[e)]	120	96(3e)

a) Reaction described in Eq. 2 under nitrogen at room temperature. b) Yield after isolation by column chromatography. The products were characterized by ^{1}H NMR and IR spectra. c) Reaction temp 89 °C. d) Unidentifiable mixture. e) Solvent pyridine was used instead of Et_3N.



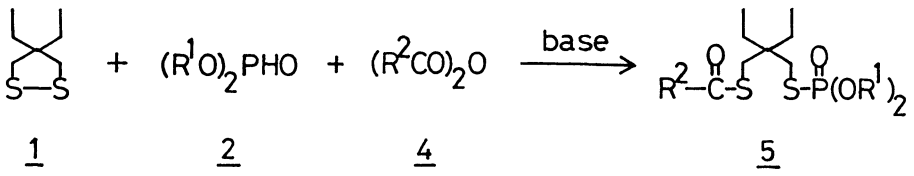
1 2 3 (2)

A further examination showed that carboxylic anhydrides do not interfere with the reductive phosphorylation, while the mercapto group in the product 3 was concomitantly acylated (Eq. 3). The product 5 is stable to air and could be isolated by Kugelrohr-distillation in good yields (see Table 2). The concomitant acylation of 3 suppresses the secondary alkyl transfer reaction

Table 2. Reactions of 4,4-Diethyl-1,2-dithiolane with Dialkyl Phosphites and Acylating Reagents[a)]

1(mmol)	2,R^1(mmol)	4,R^2(mmol)	Base(mmol)	Solvent(ml)	Time/min	Yield/%(5)[b)]
6.22	Me,9.52	Me,9.24	(TEA,37)	TEA,5.2	30	90(5a)
6.27	Et,9.39	Me,9.24		TEA,5.2	35	90(5b)
6.25	i-Pr,9.37	Me,9.24		TEA,5.2	190	86(5c)
6.40	Bu,9.31	Me,9.24		TEA,5.2	195	98(5d)
3.10	Et,4.68	Et,4.62	(TEA,18)	TEA,2.5	60	87(5e)
3.12	Et,4.62	i-Pr,4.62		TEA,2.5	65	79(5f)
3.12	Et,3.70	Ph,3.70	TEA,10.7	C_6H_6,2.0	90	76(5g)
3.04	Et,3.73	Me,4.62	K_2CO_3,6.16	THF,1.5	27h	82(5b)
3.04	Et,3.73	Me,4.62	DBU,6.16	THF,1.5	120	82(5b)
2.92	Et,4.62	Me,4.62	TEA,6.16	THF,1.5	50	88(5b)

a) Reaction described in Eq. 3 under nitrogen at room temperature. b) Isolated yields. The products were fully characterized by ^{1}H NMR and IR spectra.



1 2 4 5 (3)

described above. Neither diphosphoryl nor diacyl derivatives of the reduced 1 could be detected in the products. The use of acid halides instead of acid anhydrides was not appropriate because they reacted with phosphites prior to the reductive phosphorylation. The solvent TEA could be replaced by cyclohexane, ether, dichloromethane, pyridine, acetone, DMF, DMSO, benzene and THF, if excess TEA (>2 times molar excess of 2) was added in the mixture. Alcoholic solvents could also be used for the reductive phosphorylation but the second acylation became ineffective. The polar solvents slightly accelerated the reaction. Potassium carbonate and diazabicycloundecene (DBU) activated the phosphites, but calcium carbonate, pyridine and sodium acetate did not.

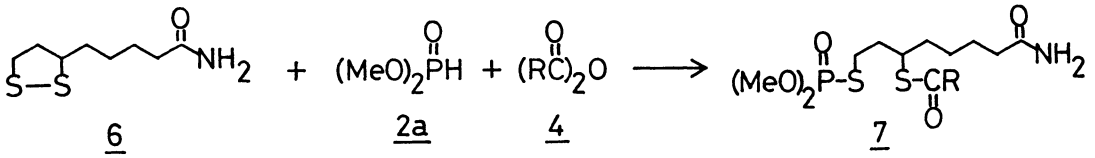
Finally, lipoamide was reacted with dimethyl phosphite and carboxylic anhydride in THF to give regioselectively 6-S-acyldihydrolipoamide derivatives bearing dimethyl phosphoryl group on 8-S atom by one-pot technique (see Table 3 and Eq. 4): A suspension of 1 mmol lipoamid 6 in 2 ml THF containing 2 mmol $(MeO)_2PHO$, 2 mmol TEA and 2 mmol acid anhydride was stirred under argon at room temperature for 2 h. The lipoamide disappeared within 60 min. After acidifying with 30% H_2SO_4, the mixture was extracted with CH_2Cl_2, and chromatographed on Fuji-gel CQ-3 (spherical type silica-gel). CH_2Cl_2-acetone(6:4) elution gave the product 7a-c.

The high regioselectivity of the present reactions is very important, since

Table 3. Reaction of Lipoamide with Dimethylphosphite and Acid Anhydrides[a)]

4,R(mmol)	TEA(mmol)	Time/min[b)]	Product, R	Yield/%[c)]
Me, 2.00	2.00	50	7a, $-CH_3$	98
i-Pr, 2.00	2.00	60	7b, $-CH(CH_3)_2$	86
Ph, 2.00	2.00	50	7c, $-C_6H_5$	92

a) Reaction described in Eq. 4: 6(1.00 mmol) and 2a(2.00 mmol) was reacted in 2.0 ml THF containing TEA and 4 at room temperature under argon for 2h. b) Time required for disappearance of 6. c) The products were fully characterized by ^1H NMR(60 and 90 MHz) and ^{13}C NMR.



6 2a 4 7 (4)

it opens a route to the selective preparation of 6-S-acyldihydrolipoyl derivatives (7) of biological interest. The selectivity at 8-S itself is not unprecedented, since a reaction of lipoic acid and trimethyl phosphite had been reported to occur regioselectively on 8-S-atom.[6)]

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