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Reaction of 4,4-Diethyl-1,2-dithiolane with Grignard Reagents

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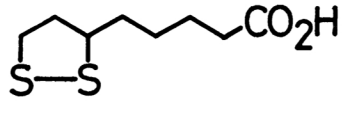
Clean ring cleavage of 1,2-dithiolane by carbanion was first recognized for 4,4-diethyl-1,2-dithiolane (3) in the reaction with Grignard reagents, the reactivity being attributed to the low polymerizing tendency of 3, similar to that of the enzyme-bound lipoic acid.

Lipoic acid (1) is found in a variety of living organisms. One of the most important role of the acid is to mediate an acetyl transfer from pyruvate to coenzyme A. Generally accepted mechanism delineated by Breslow[1] and by Ingraham[2] involves a nucleophilic S-S bond cleavage of lipoic acid by a carbanion of 2-(1-hydroxyethyl)thiazolium derivative, so-called "active aldehyde" bound to thiamine.

The S-S bond cleavage of open-chain disulfide by carbanion is well known.[3] The ring-strain of 1,2-dithiolane, about 4 - 6 kcal/mol, seemed to further support the proposed mechanism.[4] Recent works on lipoic acid derivatives, however, revealed a problem, i.e., unexpectedly low reactivity of the 1,2-dithiolane moiety toward carbaions.

A model compound of active aldehyde (2) reacts with linear dialkyl disulfides to give the expected thiol acetates and thiols in moderate yields, but is completely unreactive to methyl lipoate under the similar conditions.[5] Methylmagnesium iodide is unreactive to lipoic acid. Excess methyllithium and dimethylcuprate react to give ring-opened, methylated products but in only low yields up to 12.2%.[6] On the other hand these carbanions seem much more reactive to linear dialkyl disulfides.[3] Thus, the mechanistic basis of lipoic acid-mediated reaction in living organisms yet remains unresolved. The problem



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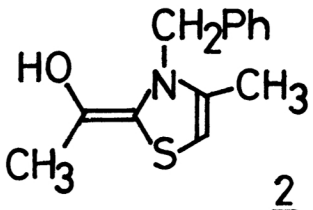
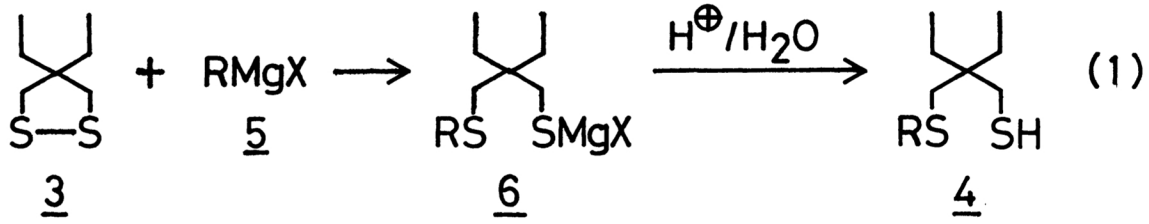


2

is much involved. We felt we had to go back to more simple system, and found that a simple 1,2-dithiolane 3 at least do react with Grignard reagents in a quantitative manner as described in Eq. 1.

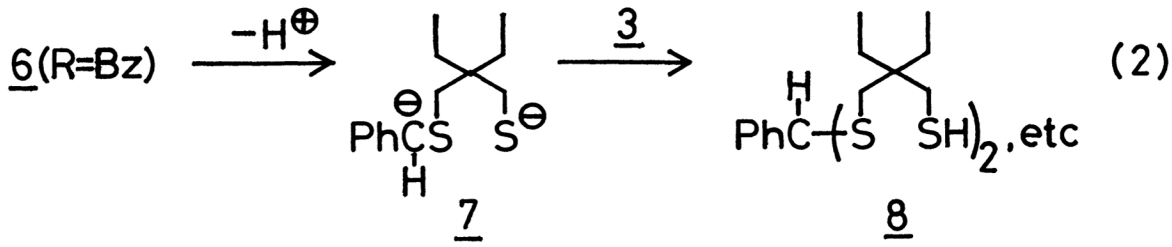


3 6 4

A typical reaction procedure is as follows. Diethyldithiolane (3)[7] 2.98 mmol was added to a stirred solution of 3.85 mmol i-PrMgBr in 20 ml ether with ice-cooling under nitrogen. Yellow color of the dithiolane dissappeared after 30 min. After addition of 10 mmol hydrochloric acid, the mixture was extracted twice with ether, washed with aqueous sodium chloride, and dried over sodium sulfate. Kugelrohr distillation under reduced pressure gave 0.539 g of 2-ethyl-2-(isopropylthiomethyl)butanethiol (**4e**, R=i-Pr), yield 88%.

Various Grignard reagents were reacted to give 4 and the results are summarized in Table 1. Primary, secondary and aryl magnesium halides gave **4a**-**g** in excellent yields and in high purity. A direct GLC analysis of the reaction mixture after hydrolysis showed that the yields of 4 were 98% or more except for **4d** and **4h**, the yields of which were yet not lower than 95%. No di-S- nor non-S-substituted propanedithiols were detected in the products. Thus, the reaction does not only represent the first clean nucleophilic S-S cleavage of 1,2-dithiolane ring but also provides a facile, selective route to the synthesis of mono- and unsymmetrically di-S-substituted 1,3-propanedithiols.

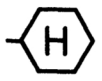
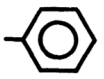
Slightly excess t-BuMgCl gave **4h** contaminated with unidentifiable by-products but this could be eliminated when a large excess of t-BuMgCl was reacted. Benzyl magnesium chloride also gave a contaminated product even if a large excess of the reagent was used. This suggests that the initially formed thiolate 6 (R=$PhCH_2$ or Bz) is deprotonated by the Grignard reagent to dianion such as 7 which further reacts with remaining dithiolane 3 to produce unstable higher adducts such as 8.



7 8

The ring-opening reaction of 1,2-dithiolanes with carbon nucleophiles is not well examined so far.[5,6,8] The present results are the first, clean example of the ring opening by carbanions and in line with the Breslow's and Ingraham's

Table 1. Reaction of 4,4-diethyl-1,2-dithiolane (3) with Grignard reagents

3(mmol)	5(mmol)	time/min[a]	4, R=[c]	yield/%[b]	(GLC yield/%)[d]
	MeMgI				
2.98	3.84	30	4a, $-CH_3$	86	(99)
	EtMgBr				
2.99	3.43	25	4b, $-CH_2CH_3$	83	(98)
	BuMgBr				
2.98	3.80	30	4c, $-(CH_2)_3CH_3$	100	(98)
	i-BuMgBr				
2.98	3.85	30	4d, $-CH_2CH(CH_3)_2$	86	(95)
	i-PrMgBr				
2.98	3.85	30	4e, $-CH(CH_3)_2$	88	(99)
	c-HexMgBr				
2.98	3.90	25	4f, 	81	(99)
	PhMgBr				
2.98	4.00	25	4g, 	89	(99)
	t-BuMgCl				
2.98	3.85	35	4h, $-C(CH_3)_3$	-	(95)
2.98	7.50	35	4h, "	85	(-)

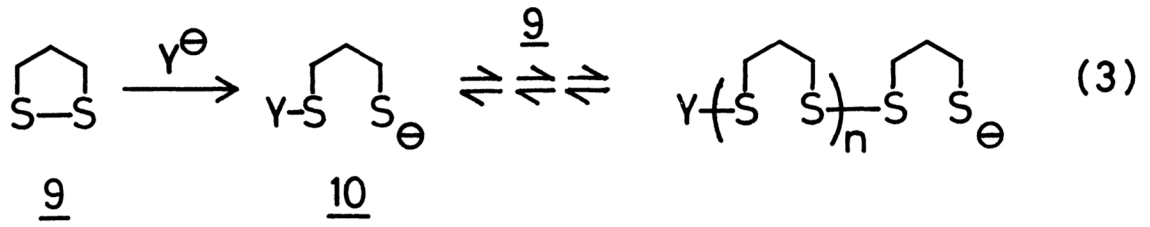
a) Reaction under ice-water cooling. Solvent: ether 20 ml. b) Isolated yield. c) The products were fully characterized by IR and NMR spectra. d) Calibration of GLC was made by using redistilled pure products.

mechanism on the acetyl transfer mediated by lipoic acid.

The present dithiolane 3 appears strikingly different from lipoic acid which has been reported as unreactive to excess methylmagnesium iodide.[6] This is probably due to the low polymerizing tendency of 3. In our experience, the polymerization is greatly affected by the substituents on C-4 in 1,2-dithiolane ring. The dithiolane 3 could be purified up to 99.5% by spinning band column distillation, and does not polymerize on standing for several months even in the presence of daylight. The ceiling temperature of ring-opening polymerization is assumed near or just above room temperature for the dithiolane 3 which is different from the other dithiolanes involving lipoic acids.[4c] Isolated 4-ethyl-4-methyl-1,2-dithiolane polymerized at room temperature within a day, and

the polymer became monomeric on storage at about 80 °C. 4,4-Dimethyl-1,2-dithiolane could not be prepared in fully monomeric form, the polymer not depolymerizing at 100 °C. Calvin et al., reported that parent dithiolane itself could be prepared only in solutions due to polymerization.[9)]

The enzyme-bound lipoic acid cannot polymerize. Under non-enzymatic conditions, however, a nucleophilic S-S bond cleavage of 1,2-dithiolane **9** generally gives a thiolate anion **10** which can react rapidly with the neighboring unreacted 1,2-dithiolane.[4a)] This results in a serious polymerization at early stage of the nucleophilic reaction, if the ring-opening polymerization is thermodynamically favored. Thus, in order to elucidate the nucleophilic reactivity of dithiolanes, the competitive polymerization must be minimized so that the target reaction is observable. Dithiolane **3** is suitable for this purpose and should serve as a simple and convenient model for enzyme-bound lipoic acid, although the reactivity may be slightly modified and lowered due to 4,4-diethyl substitutions.



9 **10** (3)

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