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REGIOSELECTIVITY OF β-VINYL-β-PROPIOLACTONE TOWARD VARIOUS NUCLEOPHILES

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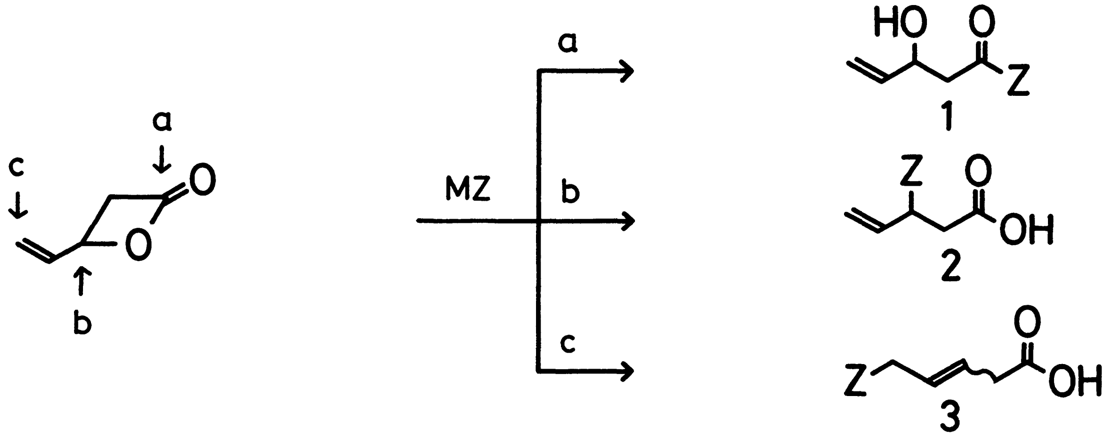
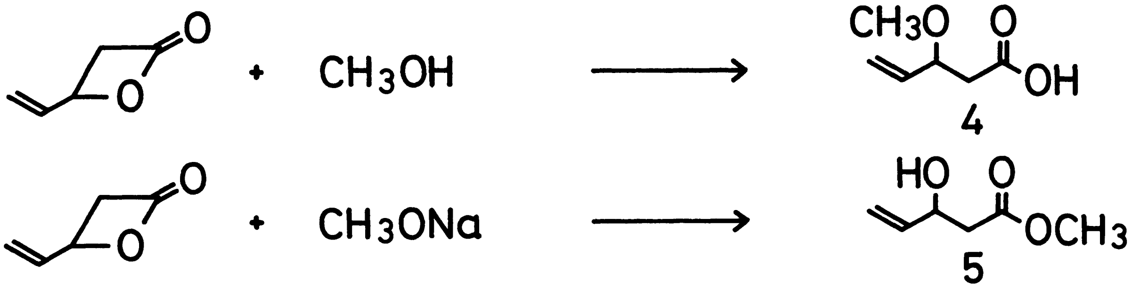
Regioselectivity in the reaction of β-vinyl-β-propiolactone with various nucleophiles was found to depend on the hard and soft acid and base (HSAB) principle. A hard base such as methoxide ion attacked the acyl carbon exclusively, while the nucleophilic attack of soft bases such as iodide and dialkyl cuprate preferred the terminal vinyl carbon to the β-carbon.

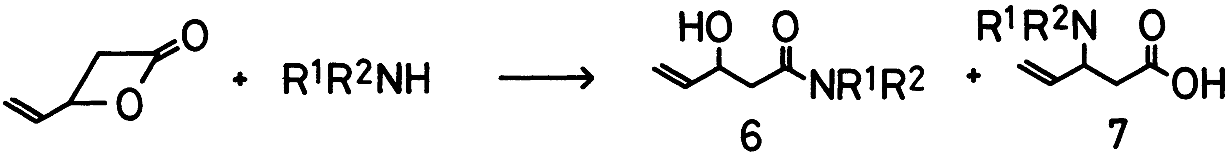
In the reaction of the compounds with two or more reactive sites, such as α,β-unsaturated carbonyl compounds, epoxides, allylic compounds, etc., the regioselectivity is one of very important problems for organic synthesis. There are a large number of reports concerning the reaction of these compounds with nucleophiles. β-Propiolactone, one of these compounds and a strained four-membered lactone, has been known to react easily with a large number of nucleophiles through ring opening.[1] Nucleophilic attack takes place either the β-carbon or the acyl carbon of β-propiolactone, and the mode of the ring opening depends on the nature of nucleophiles and experimental conditions. On the other hand, β-vinyl-β-propiolactone, which corresponds to an allylic ester, has three reaction sites toward nucleophiles, i.e., the acyl carbon, the β-carbon (S_N2 type) and the terminal vinyl carbon (S_N2' type), leading to 3-hydroxy-4-pentenoic acid derivative (1) (path a), 3-substituted 4-pentenoic acid (2) (path b), and 5-substituted 3-pentenoic acid (3) (path c), respectively. Since it has a strained four-membered lactone, it is expected to have higher reactivity than general allylic ester. In spite of enormous literatures on β-propiolactone, there are only two reports on the ring opening reaction of β-vinyl-β-propiolactone with nucleophiles such as an S_N2 type reaction with methanol in the presence of a palladium catalyst[2] and an S_N2' type reaction with organocopper reagents.[3] We wish to describe here the reaction mode of β-vinyl-β-propiolactone toward various nucleophlies.



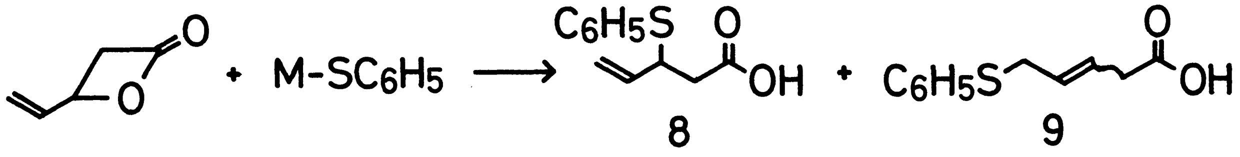
As nucleophiles of hetero atoms such as oxygen, nitrogen, sulfur, and halogen atoms, methanol, pyrrolidine and aniline, benzenethiol, and lithium halides such as lithium chloride, bromide and iodide were employed. The results were summarized in Table I. The lactone reacted with methanol at room temperature for 24 h to give only the S_N2 type product 4[4] in 80% yield. While the reaction of sodium methoxide with the lactone at 0 °C for 0.5 h followed by quenching with 1N HCl aqueous solution afforded exclusively the ester 5 in a high yield of 95%, produced by the addition to the acyl carbon (path a). The reaction of the lactone with amines in MeCN at room temperature gave a mixture of the hydroxy amide 6 and the amino acid 7 produced by the addition to the acyl carbon (path a) and by the S_N2 type reaction



(path b), respectively. Pyrrolidine gave a mixture of 6 and 7 in 61% yield with the ratio of ca. 1, while aniline gave mainly the amino acid 7, and the ratio of 7 to 6 is ca. 5 in a total yield of 77% (entries 3 and 4).

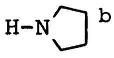


On the other hand, the reaction of the lactone with benzenethiol at room temperature for 38 h gave almost equal amount of 8 and 9 in 32% yield, produced by the S_N2 type reaction (path b) and by the S_N2' type reaction (path c), respectively. In the case of the reaction with the thiolate anion, followed by quenching with 1N HCl aqueous solution, the product ratio of 9 to 8 was found to depend on the kind of metal cation (entries 6,7, and 8). Sodium thiophenoxide gave 8 and 9 in 92% yield with the ratio of ca. 0.5. When chloromagnesium thiophenoxide, prepared from s-BuMgCl and benzenetiol in THF, was used in the presence of copper(I) iodide as a catalyst, the ratio is ca. 1 in a total yield of 95%. The ratio increased to ca. 3 by the use of copper(I) trimethyl phosphite[5] as the metal cation.



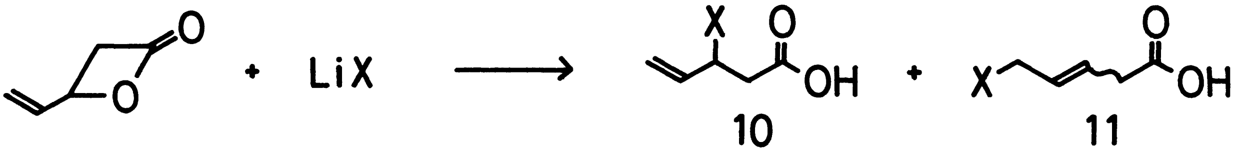
The reaction of the lactone with the halide ion of lithium salt in THF at room temperature gave also the S_N2 type and/or the S_N2' type reaction products. Lithium chloride gave mainly 10 in a yield of 56% along with a small amount of 11 in a yield of 2%. Lithium bromide gave 10 and 11 in 48% yield and the ratio of 11 to 10

Table I. Reaction of β-Vinyl-β-Propiolactone with Nucleophiles[a]

Entry	M-X	Solvent	Temp. (°C)	Time (h)	Product (yield%) 1	2	3
1	H-OCH_3	MeOH	rt	24	-	80	-
2	Na-OCH_3	MeOH	0	0.5	95	-	-
3	 [b]	MeCN	rt	1.5	32	29	-
4	H-NHC_6H_5[b]	MeCN	rt	15	13	64	-
5	H-SC_6H_5	THF	rt	38	-	17	15
6	Na-SC_6H_5	THF	0	1	-	62	30
7	ClMg-SC_6H_5[c]	THF	0	2	-	45	50
8	$(CH_3O)_3PCu$-SC_6H_5[d]	THF	0	3	-	17	54
9	Li-Cl	THF	rt	3	-	56	2
10	Li-Br	THF	rt	3	-	27	21
11	Li-I	THF	rt	1	-	-	85

[a] All reactions were carried out on 2 mmol scales in a solvent of 6 ml, and the lactone was added to the solution of M-X unless otherwise noted. [b] Amine was added to the lactone. [c] Copper(I) iodide (2 mol%) was added. [d] Prepared *in situ* by mixing copper(I) iodide, trimethyl phosphite, lithium benzenethiolate.

is ca. 0.8. Lithium iodide gave only 11 in a high yield of 85% (entries 9,10, and 11).



As mentioned above, the mode of ring opening of β-vinyl-β-propiolactone was found to depend on the nature of nucleophiles. The reaction product at the β-carbon of β-vinyl-β-propiolactone increases according to the following order, $MeO^- <$ MeOH, aliphatic amine<aromatic amine. In the case of the thiolate anion, reaction product at the terminal vinyl carbon increases according to the following pattern, $Na^+ < Mg^+ < Cu^+$. In the case of halide ion, the same tendency was observed according to the following order, $Cl^- < Br^- < I^-$. The regioselectivity is often explained by the hard and soft acid and base (HSAB) principle which was propounded by Pearson.[6] In this case, the order consists with the softness of nucleophile.[7] A hard base such as methoxide ion attacked exclusively the acyl carbon, while the nucleophilic attack of soft base preferred the terminal vinyl carbon to the β-carbon. Methanol and amines gave none of the S_N2' type reaction products, while soft base such as benzenethiol gave the S_N2' type reaction product. Lithium chloride gave the S_N2 type reaction product mainly, while soft base of lithium iodide gave the S_N2' type reaction product exclusively. These facts seem to indicate that the softness of the reaction sites of β-vinyl-β-propiolactone increases in the following order of the acyl carbon, the β-carbon and the terminal vinyl carbon.

In the reaction of β-vinyl-β-propiolactone with organometallic compounds, the mode of ring opening was also found to depend on the metal cation of organometallic compounds as shown in Table II. The reaction of the lactone with butylmagnesium bromide in the absence of a catalyst gave products through path a such as 12 and 13 mainly along with 14 and 15, produced both by the S_N2 and S_N2' type reactions, respectively, in low yields. The reaction of the lactone with butylcopper tributylphosphine complex[8] gave 14 and 15 (E:Z = 66:34) in 99% yield with the ratio of ca. 1. While soft base of diorganocuprate[9] preferred to attack at the terminal vinyl carbon of β-vinyl-β-propiolactone giving 15 (E:Z = 90:10) in a high yield.[3] Analogous result was obtained by the copper(I) catalyzed reaction of the lactone with the Grignard reagents.[3] Accordingly, β-vinyl-β-propiolactone can be used as a favorable building block for the five carbon homologation with functional groups of double bond and carboxyl group, when soft carbanion of copper reagents was used.

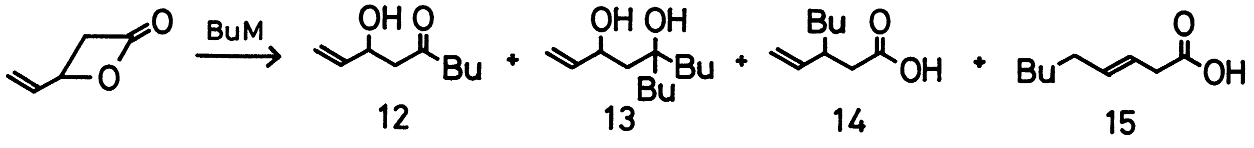


Table II. Reaction of β-Vinyl-β-Propiolactone with Organometallic Compounds[a]

BuM	Solvent	Temp. (°C)	Time (h)	Total Yield (%)	Product Ratio 12	13	14	15
BuMgBr[b]	THF	-30	0.25	36	47	22	3	28
$BuCu\cdot PBu_3$[c]	Ether	-30	1	99	-	-	54	46
BuMgBr, cat. CuI	$THF-Me_2S$	-100	0.25	94	-	-	<1	>99
$Bu_2CuMgBr$	$THF-Me_2S$	-78	1	87	-	-	1	99

[a] All reactions were carried out on 2 mmol scales, the molar ratio of BuM and the lactone is 1.2: 1.0. [b] This reaction gave some other products such as 2,4-pentadienoic acid (10%) and nona-1,3-dien-5-one (7%). [c] Prepared *in situ* by mixing copper(I) iodide, tributylphosphine, BuLi in 1:3:1 molar ratio.

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