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Novel Synthesis of Macrocyclic Lactones from ω-Carboxyalkylsulfonium Salts

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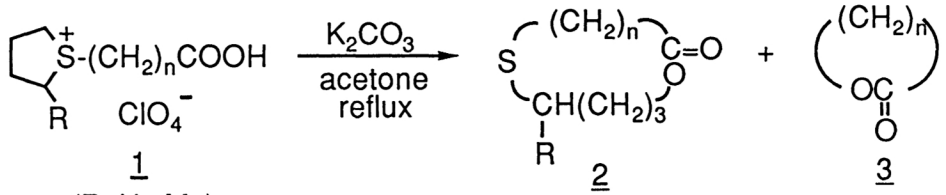
An intramolecular cyclization of S-(ω-carboxyalkyl)thiolanium salts took place readily under weakly basic conditions to afford sulfur-containing macrocyclic lactones in good yields.

A variety of synthetic methods of macrocyclic lactones have been developed up to date,[1] since these compounds have interesting biological activities and are useful as perfumes. The prevalent approach to construct simple macrocyclic lactones is the cyclization of an ω-hydroxycarboxylic acid derivative by some transesterification procedure or the cyclization of an ω-halocarboxylic acid under high-dilution conditions to prevent polymerization due to intermolecular interactions.

We have been interested in the use of cyclic sulfur compounds for the synthesis of interesting natural compounds and also in search of new synthetic fragrant compounds.[2] It has been found that alkylsulfonium salts act as good alkylating agents for carboxylate anions.[3] Especially, in case of five-membered sulfonium salts, nucleophiles preferentially attack on α-methylene carbon atom of five-membered ring.[4] We synthesized S-(ω-carboxyalkyl)thiolanium salts 1 from ω-iodocarboxylic acids and tetrahydrothiophene or 2-methyltetrahydrothiophene in the presence of silver perchlorate in acetonitrile, and investigated intramolecular cyclization of 1. We wish to report here that an intramolecular cyclization of 1 takes place readily under weakly basic conditions to give sulfur-containing macrocyclic lactones in good yields.



1
(R=H, Me)

2 3

1a: R=H, n=10
1b: R=H, n=11
1c: R=H, n=13
1d: R=Me, n=10
1e: R=Me, n=11
1f: R=Me, n=13

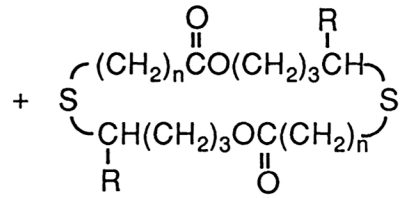


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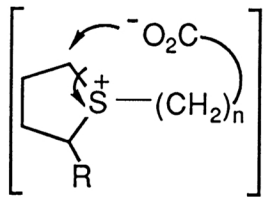
Table 1. Macrocyclic Lactones from Sulfonium Salts 1

1		Ring size	Yield/%[a]		
n	R	of 2	2	3	4
10	H	17	86	3	8
11	H	18	81	10	2
13	H	20	80	8	1
10	Me	17	82	4	4
11	Me	18	72	7	4
13	Me	20	77	14	5

a) Isolated yield.



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A typical reaction procedure is as follows. Sulfonium salt 1a (n=10, R=H) (2 mmol) dissolved in acetone (100 ml) was added slowly to a stirred suspension of potassium carbonate (6 mmol) in refluxing acetone (100 ml) over a period of 2 days to yield lactones 2a (86%), 3a (3%), and 4a (8%), respectively.[5)]

As indicated in Table 1, sulfur-containig lactones 2 were obtained in good yields together with minor amounts of by-products 3 and 4. In case of R=Me, carboxylate anion attacked regiospecifically on α-methylene carbon atom of the five-membered ring of 5 to afford lactones 2 in good yields. This simple method gives ring expansion products, sulfur-containing lactones 2, through the one-step insertion of a carboxylate anion into a cyclic -S-CH(R)$CH_2CH_2CH_2$- system in good yields. Interestingly, sulfur-containing 17-membered lactones 2 (n=10) have a musk odor.[6)]

On the other hand, an intramolecular cyclization of ω-carboxyalkyldiphenylsulfonium salts, Ph_2S^+-$(CH_2)_n$COOH ClO_4^- (n=10-14), took place readily to give 12- to 16-membered lactones 3 (85-92%) under similar reaction conditions.

The present intramolecular cyclization of (ω-carboxyalkyl)sulfonium salts is very useful for the synthesis of macrocyclic lactones. Further investigation of the scope of this novel approach to the synthesis of macrolides is in progress.[7)]

References

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2) H. Matsuyama, Y. Miyazawa, Y. Takei, and M. Kobayashi, J. Org. Chem., 52, 1703 (1987).
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4) E. L. Eliel, R. O. Hutchins, R. Mebane, and R. L. Willer, J. Org. Chem., 41, 1052 (1976); M. E. Garst and B. J. McBride, ibid., 48, 1362 (1983).
5) Treatment of 1a (n=10, R=H) (1 mmol) with potassium carbonate (3 mmol) in boiling acetone (20 ml) for 1 day gave lactones 2a (24%) and 4a (16%), respectively.
6) V. N. Belov, N. P. Solv'eva, T. A. Rudol'fi, and I. A. Voronina, Zh. Org. Khim., 1, 546 (1965).
7) Satisfactory analytical and spectral results were obtained for all the compounds described in this paper.

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