NOVEL BROMOLACTONIZATION USING A DIMETHYL SULFOXIDE-TRIMETHYLSILYL BROMIDE-AMINE SYSTEM; UNUSUAL CIS-ADDITION OF TRANS-6-SUBSTITUTED 3-CYCLOHEXENE-1-CARBOXYLIC ACIDS

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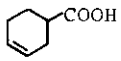
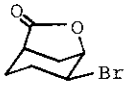
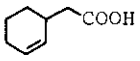
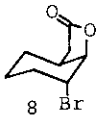
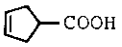
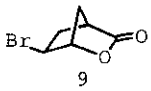
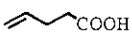
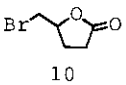
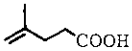
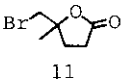
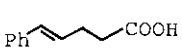
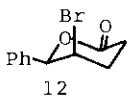
Abstract — A novel method for bromolactonization using a dimethyl sulfoxide-trimethylsilyl bromide-amine system and the first example for halolactonization in the mode of cis-addition are described.

Bromolactonization is a very useful method for regio- and stereoselective functionalization of the double bond and has been prominently applied to the organic synthesis.[1] Available procedures include the treatment of an unsaturated carboxylic acid or metal carboxylate (sodium[2a,b] or thallium[2c,d]) with an electrophilic bromonium ion source (bromine,[2a-f] sodium hypobromite,[2g] N-bromoimides or N-bromoamides,[2b,e,h-l] N-bromohydantoins,[2m-o] acyl hypobromites[2p,q]). Here, we report a novel method for bromolactonization using a dimethyl sulfoxide (DMSO)-trimethylsilyl bromide (TMSBr)-amine system and the characteristic feature of this method.

Recently, a number of biologically active halogenated terpenes, which have a bromocyclohexane ring system as a part of their structures, have been isolated from marine organisms.[3] In connection with our synthetic studies on biologically active halogenated marine terpenes, we have investigated bromolactonization of cyclohexenecarboxylic acid derivatives as a step for the stereoselective construction of the bromocyclohexane ring system. Pagnoni and co-workers have reported α-halogenation of ketones and aldehydes using a DMSO-trimethylsilyl bromide or chloride system as a new type of halonium ion sources which may contain S-X (X=Br or Cl) bond.[4] Attempts to effect bromolactonization of the cyclohexenecarboxylic acid (1) with DMSO and TMSBr under conditions, which were successful for α-halogenation of ketones and aldehydes,

Table 1. Bromolactonization of Unsaturated Carboxylic Acids

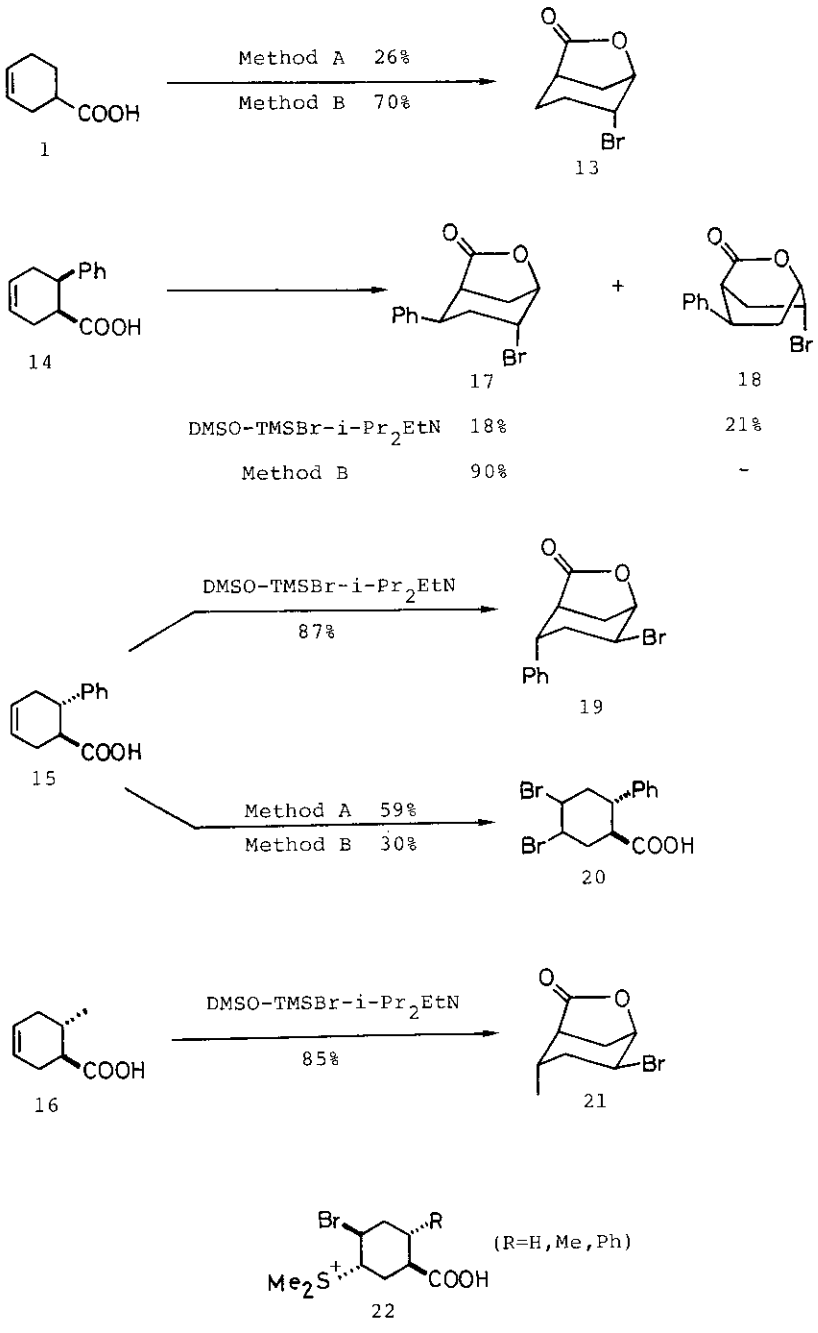
Unsaturated Carboxylic Acid	Solvent	Amine	Time (h)	Product	(Yield %)
 1	CH_2Cl_2	Et_3N	72	 7	(37)*
	CH_2Cl_2	Et_3N	12		(54)
	CH_2Cl_2	i-Pr_2EtN	10		(54)
	MeCN	i-Pr_2EtN	12		(49)
	$CHCl_3$	i-Pr_2EtN	12		(55)
 2	$CHCl_3$	Et_3N	12	 8	(41)
	$CHCl_3$	i-Pr_2EtN	12		(45)
 3	$CHCl_3$	Et_3N	12	 9	(29)
	$CHCl_3$	i-Pr_2EtN	12		(40)
 4	$CHCl_3$	Et_3N	12	 10	(29)
	$CHCl_3$	i-Pr_2EtN	12		(23)
 5	$CHCl_3$	Et_3N	12	 11	(52)
	$CHCl_3$	i-Pr_2EtN	12		(60)
 6	$CHCl_3$	Et_3N	5	 12	(41)
	$CHCl_3$	i-Pr_2EtN	5		(50)

* Reaction was carried out at room temperature.

were unsuccessful. But in the presence of triethylamine (Et_3N) or diisopropylethylamine (i-Pr_2EtN), the lactone could be obtained. The best result was obtained when the reaction was carried out in chloroform ($CHCl_3$) and under reflux. The results for some unsaturated carboxylic acids (**1-6**) are given in Table 1 and typical procedure is as follows. To a stirred solution of DMSO (0.11 ml, 1.6 mmol) in $CHCl_3$ (3 ml) at 0 °C was added TMSBr (0.21 ml, 1.6 mmol) and stirring was continued for 30 min at the same temperature. A $CHCl_3$ (1 ml) solution of an unsaturated carboxylic acid (1.3 mmol) and, after 10 min, amine (1.6 mmol) were added to the reaction mixture at 0 °C and the whole was stirred and refluxed for the time indicated in Table 1. Usual work-up afforded an almost pure bromolactone. The structures of the products were assigned from their ir and ^{1}H-nmr spectra and by comparison with those of the bromolactones prepared by the reported methods.

Generally, the halonium ion formed from the reaction of the unsaturated carboxylic acid with the electrophilic X^+ spieces reacts with the intramolecular carboxyl group in the mode of S_N2 reaction as well-recognized mechanism. Therefore, concerning the stereochemistry, halolactonization is considered to give a trans-adduct.[1] Unexpectedly, the cis-adduct (7[5] and 12[5]) were exclusively obtained when **1** and **6** were used. In the case of **6**, the δ-lactone **12** was also obtained by the reported methods (method A: bromine-aqueous sodium bicarbonate[2a] and method B: lead tetraacetate-zinc bromide[2q]). Therefore, **12** might be produced via the same more stable benzylic cation intermediate. On the other hand, bromolactonization of **1** by the same methods afforded the usual trans-γ-lactone (**13**) (Scheme 1). Thus, we examined with cis-6-phenyl-, trans-6-phenyl-, and trans-6-methyl-3-cyclohexene-1-carboxylic acids (**14**, **15**, and **16**). Bromolactonization of **14**, having an axially oriented carboxyl group, by our method afforded the γ- and δ-lactones (**17** and **18**), both of which were trans-adducts. By the method **B**, **13** was exclusively converted to the trans-γ-lactone (**17**). On the other hand, bromolactonization of the trans-6-substituted derivatives (**15** and **16**), both of which have an equatorially oriented carboxyl group, stereoselectively afforded the cis-adducts (**19** and **21**), respectively in good yield by our method, while **15** predominantly afforded the dibromocarboxylic acid (**20**) by the methods A and B.

To our knowledge, this is the first example for halolactonization in the mode of cis-addition. It is also noticeable that the equatorially oriented carboxyl group, which is sterically unfavourable for participation, cyclized to the lactone in good yield. Although this reaction seems to proceed via the sulfonium intermediate (**22**), details are not clear. Further study on reaction mechanism is now under investigation.


Method A 26%
Method B 70%
1
13
14
17
18
+
DMSO-TMSBr-i-Pr2EtN 18% 21%
Method B 90% -
DMSO-TMSBr-i-Pr2EtN
87%
15
19
Method A 59%
Method B 30%
20
DMSO-TMSBr-i-Pr2EtN
85%
16
21
(R=H,Me,Ph)
22

Scheme 1

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3. J. D. Martin and J. Darias, 'Marine Natural Products: Chemical and Biological Perspectives' **Vol. 1**, ed. by P. J. Scheuer, Aademic press, New York, 1978, p. 125; K. L. Erickson, ibid., **Vol. 5**, 1983, p. 131; D. J. Faulkner, Nat. Prod. Rep., **1984**, 251; **1986**, 1.
4. F. Bellesia, F. Ghelfi, R. Grandi, and U. M. Pagnoni, J. Chem. Res. (S), **1986**, 426; 428.
5. **7**: Ir (ν, cm^{-1}, $CHCl_3$) 1780. ^{1}H-Nmr (δ, ppm, $CDCl_3$) 4.16 (dd, J=10.6, 6.4 Hz, CHBr), 4.92 (d, J=6.0 Hz, CHO). **12**: Ir (ν, cm^{-1}, $CHCl_3$) 1740. ^{1}H-Nmr (δ, ppm, $CDCl_3$) 4.37 (ddd, J=4.8, 6.2, 6.2 Hz, CHBr), 5.52 (d, J=6.2 Hz, CHO).

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