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Preliminary communication

A novel intramolecular cyclization reaction. Synthesis and properties of 5- and 8-membered germalactones

Yedi Guan *, Jiwen Zou, Zhengguo Zhu

Department of Chemistry, Peking University, Beijing 100871, People's Republic of China

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Abstract

A series of 5- and 8-membered germalactones are synthesized via the thermal or Raney-Ni catalyzed intramolecular dehydrogenation coupling reaction (M. Massol, J. Barrau, J. Satge and B. Bouyssieres, *J. Organomet. Chem.*, *80* (1974) 47) between the Ge–H and CO_2H groups. The physical and chemical properties of these compounds are described.

Keywords: Germanium; Lactones; Synthesis and properties

1. Introduction

The synthesis of germa-γ-lactones from monobrompropanoic acid and their morphine-like activity have been reported [1]. In our early work on the synthesis of antitumor active organogermanium compounds we discovered that dialkyl(hydro)germylpropanoic acid and dialkyl(hydro)germyl-*N*-propanamino acid can be transformed into the corresponding 5- and 8-membered germalactones by Raney-Ni catalysis [2]. We report here that this process can be successfully adopted to the synthesis of a series of 5- and 8-membered germalactones in mild conditions and with good yields.

2. Results and discussion

The most common route to organohydrogermanes involves the reduction of the corresponding halides, oxides, etc. by lithium aluminium hydride or zinc amalgam and aqueous HCl [3,4]. However, these methods are not very effective in transforming the substituted germylpropanoic acids (including mono-, di- and trihalogermyl propanoic acid and germylpropanoic acid sesquioxide) into the corresponding hydrogermylpropanoic acid because of the sensibility of the carboxylic group to the reduction reagents. Though, while these substitutive germylpropanoic acids are treated with sodium borohydride in H_2O at 0°C, the hydrogermylpropanoic acids are obtained with good yields. Treated with Raney-Ni in THF at RT or stored in closed tube for 1.5–2 months at RT without any catalyst, the hydrogermylpropanoic acids are further transformed into the corresponding 5-membered germalactones with virtually quantitative yields. The reaction procedure is illustrated in Scheme 1 and the results are summarized in Tables 1 and 2.

The intramolecular cyclization of (**2**) was monitored by IR and ^1H NMR spectra and was demonstrated by the disappearance of the absorption band attributable to the Ge–H bond in IR and disappearance of the signal at 3.00 ~ 5.00 ppm of Ge–H in ^1H NMR.

It was considered that intermolecular dehydrogenation might also take place to give polymers. But the molecular weight determination of compounds (**3**) demonstrated that the dominating products are those of the intramolecular cyclization. Thus, we suggest the following explanation. In hydrogermylpropanoic acids, the germanium atoms have empty d orbitals while the oxygen atoms in –COOH have lone electron pairs, so most of the individual molecules might adopt the following conformation, which favors the intramolecular cyclization, especially in solution (Scheme 2).

In the synthesis of peptides, the following steps are often the effective ones:

$$\text{Z-NHCHRCO}_2\text{H} \xrightarrow[(2)\,\text{ClCO}_2\text{C}_2\text{H}_5]{(1)\,(\text{C}_2\text{H}_5)_3\text{N}} \text{Z-NHCHRCO}_2\text{CO}_2\text{C}_2\text{H}_5$$

$$\xrightarrow{(3)\,\text{H}_2\text{NCHRCO}_2\text{H}} \text{Z-NHCHRCONHCHRCO}_2\text{H}.$$

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* Corresponding author.

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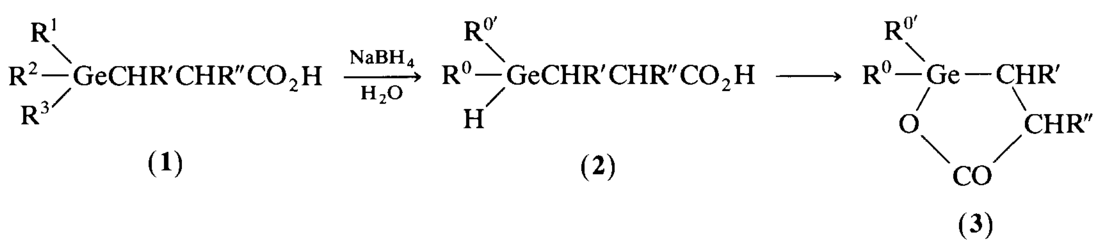
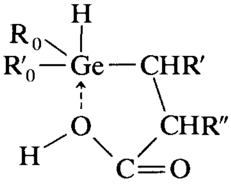


R′, R″ = H (**a**, **c**, **d**) R′ = CH_3, R″ = H (**b**) R′ = H, R″ = CH_3 (**e**)

Scheme 1.

Similar steps are taken to introduce amino acids to hydrogermyl propanoic acid **2a** and **2b**, but the expected resulting compounds are very difficult to purify owing to the sensibility of Ge–H bond to the COOH group. However, treated with Raney-Ni in THF, these compounds can be transformed into the corresponding 8-membered germalactones, which can be purified satisfactorily. Similarly molecular weight determination demonstrated that the dominative products are those of the intramolecular cyclization, which suggests that the following conformation is favored in solution (Scheme 3).



Scheme 2.

The crude product of 8-membered germalactones was purified by solution of hot THF - cyclohexane and filtered the solution through a büchner funnel, any dimer or polymer should be left behind at this point. The reaction procedure is illustrated in Scheme 4 and the results are summarized in Table 3.

All IR spectra of 5-, 8-membered germalactones show an absorption band attributable to the carbonyl group at much lower frequencies (Tables 2 and 3, 1600–1670 cm^{-1}) than the corresponding **1a–e** (Table 1, 1710–1720 cm^{-1}). Absorption band attributable to CON group in **5a–e** appears at much lower frequencies (Table 3, 1635–1650 cm^{-1}) than that of the general amide. The remarkable feature in the IR spectrum of **5a–e** suggests the presence of Ge ← N coordination bond [5], where the lone electron pair of the N atom participates in the formation of the coordination bond. As expected, the existence of a N → Ge of **5a–e** favors intramolecular cyclization reaction.

The EIMS spectrum of all the 8-membered germalactones shows molecular ion peaks with high abun-

Table 1
Reaction of compounds (1) with $NaBH_4/H_2O$

	(1)			(2)		Bp(°C)	Yield (%)	IR(cm^{-1})	
	R^1	R^2	R^3	R^0	$R^{0\prime}$			C=O	Ge–H
a	CH_3	CH_3	Br	CH_3	CH_3	86–88/4 Torr	89 [a]	1710	2030
b	CH_3	CH_3	Br	CH_3	CH_3	112–113/4 Torr	89 [a]	1713	2015
c	sesquioxide			H	H	71–72/1Torr	80 [b]	1720	2040
d	Cl	Cl	Cl	H	H	71–72/1 Torr	83 [b]	1720	2040
e	Ph	Br	Br	Ph	H	142–143/1 Torr	85 [c]	1712	2055

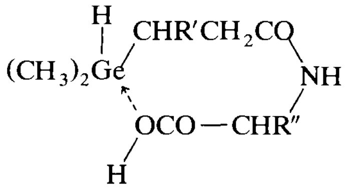
[a] **1** (1 mol) was treated with $NaBH_4$ (2.2 mol); [b] with $NaBH_4$ (4.8 mol); [c] with $NaBH_4$ (3.6 mol) in H_2O at 0°C for 1 h.

Table 2
Preparation of germa-γ-lactones

	(3)		Mp(°C)	Yield (%)	Mol. wt. found(calcd)	IR(cm^{-1})		MS ($M^+ + 1$ m/z)
	R^0	$R^{0\prime}$				C=O	Ge–H	
a	CH_3	CH_3	174–6 [a]	100	–	1650	none	177
			173–4 [b]	90		1650	none	
			145–6 [a]	100		1640	none	
b	CH_3	CH_3	144–5 [b]	85	195(190)	1640	none	
c	H	H	137–8 [a]	100	165(148)	1620	2080	149
e	Ph	H	164–6 [b]	70	269(238)	1600	2050	239

[a] The liquid compound (**2**) was stored in closed tube for 1.5–2 months at RT; [b] **2** (1 mol) was treated in THF with Raney-Ni for 15 min at RT.

dance (13.82–36.85), as well as the typical peaks of $[M-CH_3]^+$, $[M-CO_2H]^+$, $(CH_3)_2Ge^+$. The very strong peak of $(CH_3)_2Ge^+$ is generally observed as a base peak. No peaks of the dimers or polymers have been found.



Scheme 3.

3. Experimental

All the melting points were determined in a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were recorded with a Nicolet 5-MX, FT-IR. ^1H NMR spectra were determined with a Varian FT-80A spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded with a VG-ZAB-HS spectrometer. Molecular weights were determined by Rast's method. [6]

4. Materials

Trisubstituted germylpropanoic acid was prepared by a previously published procedure [2].

4.1. General procedure for the reduction of trisubstituted germylpropanoic acid (**1**)

$NaBH_4$ (0.10 mol) in water was added dropwise to a stirred solution of substituted germylpropanoic acids in water at 0°C. The mixture was stirred for 1 h. and then poured into a dilute hydrochloric acid solution. The aqueous solution was extracted with ether. The ether layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by distillation to give the expected products **2a–e** in 80–89% yields.

3-(Dimethylhydrogermyl) propanoic acid (**2a**)

B.p. 86–88°C/4 Torr. ^1H NMR ($CDCl_3$, δppm): 0.24 (d, 6H, $J=3.4$ Hz, $(CH_3)_2Ge$), 1.09 (m, 2H, CH_2Ge), 2.64 (t, 2H, $J=8.0$ Hz, CH_2CO), 3.87 (m, 1H, Ge–H), 10.43 (s, 1H, COOH) IR (cm^{-1}) 2030 (Ge–H), 1710 (C=O), 600 (Ge–C). MS. (m/z) 177 (M^+-1). Anal. found: C 33.66, H 6.58%. $C_5H_{12}GeO_2$ calcd: C 33.96, H 6.85%.

3-(Dimethylhydrogermyl)-3-methylpropanoic acid (**2b**)

B.p. 112–113°C/4 Torr. ^1H NMR ($CDCl_3$, δppm): 0.21 (d, 6H, $J=3.4$ Hz, $(CH_3)_2Ge$), 1.16 (m, 4H, CH_3CHGe), 2.39 (m, 2H, CH_2CO_2H), 3.80 (m, 1H, Ge–H), 10.50 (s, 1H, COOH). IR (cm^{-1}) 2015 (Ge–H), 1713 (C=O), 600 (Ge–C). MS. (m/z) 191 (M^+-1). Anal. found: C 37.70, H 7.39%. $C_6H_{14}GeO_2$ calcd: C 37.76, H 7.41%.

3-(Trihydrogermyl)propanoic acid (**2c**)

B.p. 71–72°C/1 Torr. M.p. 14–15°C. ^1H NMR ($CDCl_3$, δppm): 1.30 (m, 2H, CH_2Ge), 2.55 (t, 2H, $J=8.0$ Hz, CH_2CO), 3.57(t, 3H, $J=3.8$ Hz, H_3Ge), 10.64 (s, 1H, COOH). IR (cm^{-1}), 2040(Ge–H), 1720 (C=O), 630 (Ge–C). MS. (m/z) 149 (M^+-1). Anal. found: C 24.06, H 5.53%. $C_3H_8GeO_2$ calcd: C 24.23, H 5.43%.

2-Methyl-3-(dihydrophenylgermyl)-propanoic acid (**2e**)

B.p. 142–143°C/1 Torr. ^1H NMR($CDCl_3$, δppm): 1.21–1.55 (m, 5H, CH_3, CH_2Ge), 2.63 (m, 1H, CHCO), 7.25–7.50 (m, 5H, Ph), 4.45 (t, 2H, $J=3.8$ Hz, H_2Ge), 11.48 (s, 1H, COOH). IR (cm^{-1}) 2055 (Ge–H), 1712 (C=O), 640 (Ge–H).'MS. (m/z) 239 (M^+-1). Anal.

(I) NEt_3/THF and $ClCO_2CH_2CH(CH_3)_2$; (II) $NH_2CHR''CO_2H/NaOH–H_2O$; (III) $HCl–H_2O$; (IV) Raney-Ni/THF.

Scheme 4.

Table 3
Preparation of germa-ζ-lactones

	(5)		Mp(°C)	Yield (%)	Mol.wt. found(calcd)	IR(cm^{-1}) CONH	MS (M^+ m/z)
	R'	R''					
a	H	H	205 [a]	51	217(232)	1650	233
b	H	CH_3	152–4	65	250(246)	1655	247
c	H	$CH(CH_3)_2$	284–6	70	304(274)	1640	275
d	CH_3	H	210 [a]	71	272(246)	1635	247
e	CH_3	CH_3	247 [a]	70	294(260)	1640	261

found: C 50.23, H 6.10%. $C_{10}H_{14}GeO_2$ calcd: C 50.29, H 5.91%.

4.2. General procedure for the formation of germa-γ-lactones

Method (I): dialkylhydrogermylpropanoic acid was placed in closed tube for 1.5–2 months. The liquid was completely transformed into the solid product **3a–c.**

Method (II): to a solution of dialkylhydrogermylpropanoic acid in THF was added Raney-Ni. The mixture was stirred for 15 min. The solution was separated and evaporated to dryness in vacuo. The resulting solid was recrystallized from THF/cyclohexane to give the expected product **3a** [1], **3b** [1], **3e** in 70–90% yield.

4,4-Dihydro-4-germa-γ-butyrolactone (**3c**)

^{1}H NMR(CF_3COOD, δppm): 1.78 (m, 2H, CH_2Ge), 3.01 (t, 2H, $J = 7.4$ Hz, CH_2CO), 6.10 (t, 2H, $J = 3.8$ Hz, H_2Ge). IR (cm^{-1}): 2060 (Ge–H). MS. (m/z) 149 ($M^+ + 1$). Anal. found: C 24.08, H 4.10. $C_3H_6GeO_2$ calcd: C 24.56, H 4.12%.

2-Methyl-4-phenyl(hydro) germa-γ-butyrolactone (**3e**)

^{1}H NMR (CF_3COOD, δppm): 1.50 (d, 3H, $J = 8.1$ Hz, CH_3), 1.89 (m, 2H, CH_2Ge), 3.14 (m, 1H, CHCO), 6.69 (t, 1H, $J = 3.8$ Hz, HGe), 7.34–7.75 (m, 5H, Ph). IR (cm^{-1}): 2100 (G-H). MS. (m/z) 239 ($M^+ + 1$). Anal. found: C 50.37, H 5.06%. $C_{10}H_{12}GeO_2$ calcd: C 50.72, H 5.11%.

4.3. General procedure for the formation of germa-ζ-lactones

A solution of **2b** or **2a** (0.02 mol) in THF was stirred and chilled to −15°C by a ice salt bath. Triethylamine (0.021 mol) and isobutylchloroformate (0.022 mol) were added, the mixture was stirred for 15 min. Amino acid (0.03 mol) in sodium hydroxide solution was added and stirred for 1 h and then poured into a dilute hydrochloric acid solution, the aqueous solution was extracted with ether, the ether layer was separated, washed with water, dried over anhydrous $MgSO_4$, evaporated to dryness in vacuo. The resulting solid was dissolved into 50 ml of THF, Raney-Ni catalyst was added, the mixture was stirred for 15 min. The solution was separated and evaporated to dryness, to afford a crude product, purified by THF/cyclohexane, to give the expected product **5a–e** in 51–71% yields.

7.7-Dimethyl-7-germapropanoylglycinelactone (**5a**)

M.p. 205°C IR (cm^{-1}), 1656 (CO_2), 1576 (CONH), 820 (Ge–O), 620 (Ge–C). ^{1}H NMR (CF_3COOD, δppm): 1.01 (s, 6H, $(CH_3)_2Ge$), 1.77 (t, 2H, $J = 8.1$ Hz, CH_2Ge), 3.28 (t, 2H, $J = 7.4$Hz, CH_2CO) 4.44 (s, 2H, NCH_2CO). MS (m/z) 233 (M^+). Anal. found: C 36.28, H 5.80, N 6.10%. $C_7H_{13}NGeO_3$ calcd: C 36.28, H 5.65, N 6.04%.

7.7-Dimethyl-7-germapropanoylalaninelactone (**5b**)

M.p. 152–154°C IR (cm^{-1}), 1660 (CO-N), 830 (Ge–O), 620 (Ge–C). ^{1}H NMR (CF_3COOD, δppm) 1.02 (s, 6H, $(CH_3)_2Ge$), 1.65 (m, 5H, CH_2Ge, CH_3), 1.87 (t, 2H, $J = 7.4$Hz, CH_2CO), 3.28 (m, 1H, NHCHCO). MS. (m/z) 247 (M^+). Anal. found: C 38.79, H 6.30, N 5.47%. $C_8H_{15}NGeO_3$ calcd: C 39.08, H 6.16, N 5.69%.

7.7-Dimethyl-7-germapropanoylvalninelactone (**5c**)

M.p. 284–286°C IR (cm^{-1}) 1640 (CO_2), 1540 (CO-N), 830 (Ge–O), 627 (Ge–C). ^{1}H NMR (CF_3COOD, δppm) 1.02 (s, 6H, $(CH_3)_2Ge$), 1.15 (d, 6H, $J = 6.8$ Hz, $2CH_3$), 1.78 (t, 2H, $J = 8.1$ Hz, $GeCH_2$), 3.34 (t, 2H, $J = 7.4$ Hz, CH_2CO) 4.02 (m, 1H, NCHCO), 4.84 (d, 1H, $J = 4.9$ Hz, NH). MS (m/z) 275 (M^+). Anal. found: C 43.66, H 6.96, N 4.96%. $C_{10}H_{19}NGeO_3$ calcd: C 43.85, H 6.99, N 5.12%.

6,7,7-Trimethyl-7-germapropanoylglycinelactone (**5d**)

M.p. 210°C IR (cm^{-1}) 1660 (CO_2), 1540 (CO-N), 835 (Ge–O), 635 (Ge–C). ^{1}H NMR (CF_3COOD, δppm) 0.89 (s, 6H, $(CH_3)_2Ge$), 1.40 (d, 3H, $J = 8.1$ Hz, CH_3), 2.25 (m, 1H, GeCH), 3.00 (m, 2H, CH_2CO), 4.45 (s, 2H, NCH_2CO). MS. (m/z) 247 (M^+). Anal. found: C 39.10, H 6.20, N 5.49%. $C_8H_{15}NGeO_3$ calcd: C 39.08, H 6.16, N 5.69%.

6,7,7-Trimethyl-7-germapropanoylalaninelactone (**5e**)

M.p. 247°C IR (cm^{-1}) 1640 (CO_2^-), 1570 (CO-N), 830 (Ge–O), 630 (Ge–C). ^{1}H NMR (CF_3COOD, δppm) 0.98 (s, 6H, $(CH_3)_2Ge$), 1.40 (d, 3H, $J = 8.1$ Hz, CH_3), 1.52 (d, 3H, CH_3), 2.25 (m, 1H, GeCH), 3.01 (m, 2H, CH_2CO), 4.90 (m, 1H, NCH_2CO). MS. (m/z) 261 (M^+). Anal. found: C 41.50, H 6.50, N 5.26%. $C_9H_{17}NGeO_3$ calcd: C 41.59, H 6.60, N 5.39%.

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