

Preliminary communication

ORGANOGERMANIUM COMPOUNDS: FIRST SYNTHESIS OF BIOACTIVE TRITHIAGERMATRANES SUBSTITUTED WITH NOVEL FUNCTIONAL GROUPS

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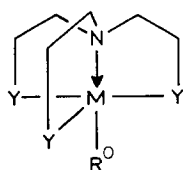
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Summary

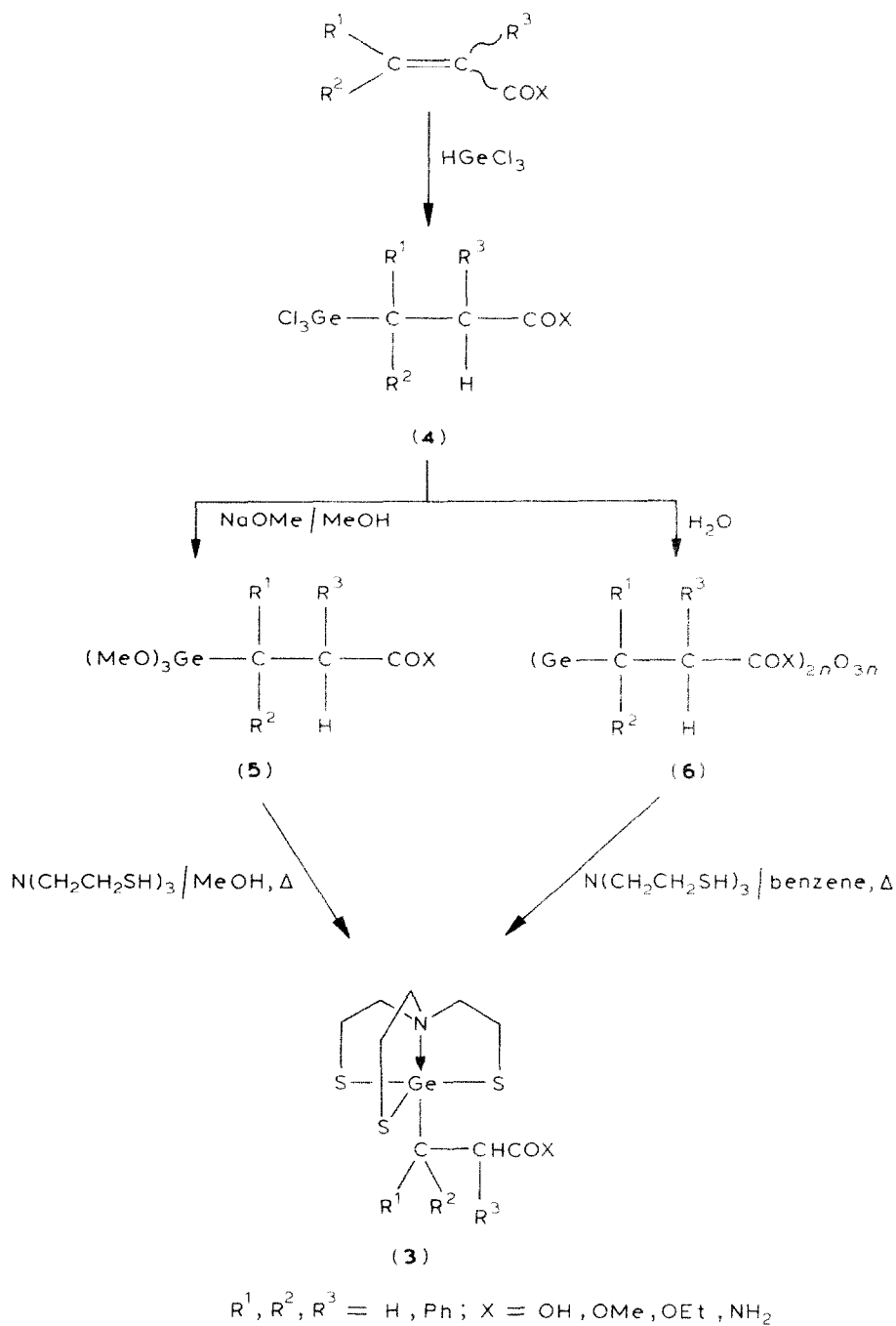
The synthesis and properties of trithiagermatranes (**3**) via reaction of tris(2-mercaptoethyl)amine with trimethoxygermyl adducts (**5**) and germanium sesquioxides (**6**) are described.

Silatrane (**1**) as compounds with metallatrane skeletons [1], have received much attention owing to their high biological activity and peculiar chemical structures [2]. The corresponding germatranes (**2**) contain germanium atoms instead of silicon atoms. However, there are not many reports on the synthesis and the biological activities of such compounds [3]. Lukevits et al. [4] recently reported carbamoyl ethyl germatrane (**2**), ($R^0 = CH_2CH_2CONH_2$) to have psychotropic and antitumor activity. Recently, we reported the simple and improved synthesis of 1-substituted germatranes [5].

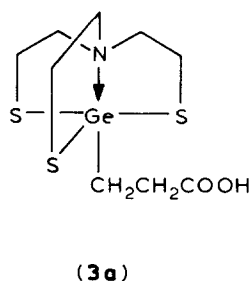
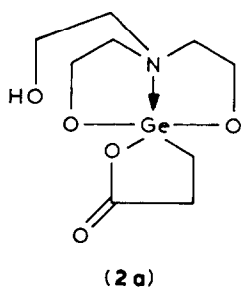
Here we present a general method for the first synthesis of 2,8,9-trithiagermatranes (**3**), which are compared with 2,8,9-oxagermatranes (**2**) with regard to their physical and chemical properties, and bioactivity



- (**1**: Y = O, M = Si ;
2: Y = O, M = Ge ;
3: Y = S, M = Ge)



SCHEME 1.



The synthetic procedure is shown in Scheme 1. First, the α,β -unsaturated compounds are treated with trichlorogermane to form trichlorogermeryl adducts (**4**) [6], which in turn form trimethoxygermyl compounds (**5**) with NaOMe in methanol. The compounds formed were allowed to react with tris(2-mercaptoethyl)amine in methanol to provide the desired products (**3**) in 44.8–61.2% yields (Method A). In Method B tris(2-mercaptoethyl)amine and germanium sesquioxide (**6**) obtained from hydrolysis of the germeryl adducts **4** were heated in benzene to form compounds **3** in 51–70% yields.

The molecular structure of the trithiagermatranes (**3**) thus obtained was determined by elemental analysis and spectral analysis (^1H and ^{13}C NMR and mass spectroscopy). For example, **3a**; IR (KBr): 1700 (C=O), 400, 370 (Ge–S) cm^{-1} ; mass spectrum (70 eV) m/e : 342 (M^+); ^1H NMR (in CDCl_3 , δ , ppm): 1.46 (2H, t, J 9.0 Hz, Ge– CH_2), 2.58 (2H, t, J 9.0 Hz, CH_2COOH), 2.70 (6H, s, NCH_2), 2.70 (6H, s, SCH_2); ^{13}C NMR (in CDCl_3 , δ , ppm) 24.65 (Ge– CH_2), 25.49 (SCH_2), 29.72 (CH_2CO), 55.73 (NCH_2), 180.07 (CO).

The results of the preparation of **3** are summarized in Table 1.

It is noteworthy that the structure of **3a** differs from that of **2a**, which was obtained from the reaction of carboxyethylgermanium sesquioxide [7] (**6a**: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$, $\text{X} = \text{OH}$) with triethanolamine instead of tris(2-mercaptoethyl)amine and was found by X-ray crystallographic analysis to be a spirogermanium compound [8] with a germocine ring. The presence of a transannular $\text{N} \rightarrow \text{Ge}$ bond was established by X-ray structure analysis for **3a**. The $\text{Ge} \rightarrow \text{N}$ distance (2.63 Å) is longer than that in the carbamoylethyl germatrane (**2**) (2.23 Å) investigated earlier [9] because of decreasing electron supply to germanium due to the low electronegativity of sulfur compared with oxygen.

TABLE 1
SYNTHESIS OF 2,8,9-TRITHIAGERMATRANES (**3**)

3	R^1	R^2	R^3	X	M.p. ($^{\circ}\text{C}$)	Method	Yield (%)	Molecular formula ^a
a	H	H	H	OH	167	B	51.0	$\text{C}_9\text{H}_{17}\text{GeNO}_2\text{S}_3$
b	H	H	H	NH_2	194	A	44.8	$\text{C}_9\text{H}_{18}\text{GeN}_2\text{OS}_3$
c	C_6H_5	H	H	NH_2	203	B	70.0	$\text{C}_{15}\text{H}_{22}\text{GeN}_2\text{OS}_3$
d	H	H	H	OCH_3	87	A	61.2	$\text{C}_{10}\text{H}_{19}\text{GeNO}_2\text{S}_3$
e	C_6H_5	H	H	OC_2H_5	105–107	A	56.3	$\text{C}_{16}\text{H}_{23}\text{GeNO}_2\text{S}_3$

^a Elemental analyses of these compounds were within acceptable limits.

Although **2a** is readily hydrolyzed to afford triethanolamine and trihydroxygermylpropanoic acid, **3a** is very stable to water. The reason for the differences in the structure and reactivity between **2a** and **3a** in going from an oxygen- to a sulfur-bonded germanium atom has not been clarified. Among these compounds, especially 3-(1'-germa-5'-aza-2',8',9'-trithiabicyclo[3.3.3]undecyl)propanoic acid (**3a**) exhibited strong inhibitory activity against dipeptidylcarboxypeptidase degrading encephalins that have morphine-like action.

Investigation of the other biological activities of these newly prepared compounds is now being carried out.

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