

ORGANOGERMANIUM COMPOUND. NEW SIMPLIFIED SYNTHESIS OF  
GERMATRANES SUBSTITUTED WITH NOVEL FUNCTIONAL GROUPS

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**Abstract** ——— New general methods for the synthesis of  
5-substituted germatranes (4) have been directly developed  
using the corresponding germyl adducts (2) obtained by germyl-  
ation of  $\alpha,\beta$ -unsaturated compounds (1) with trichlorogermane.

There has been considerable interest in recent years in the chemistry of bioactive organosilicon and germanium compounds<sup>1</sup>. However, only a few reports<sup>2</sup> have appeared on bioactive germanium compounds having unique structures and comparable to silicon in their properties. We recently observed that carboxyethylgermanium sesquioxide (Ge-132) (5;  $R^1=H$ ,  $R^2=COOH$ ) and related compounds formed from the hydrolysis of  $\beta$ -trichlorogermylpropionic acid and its derivatives (germyle adducts) (2) obtained from a reaction of readily available  $\alpha,\beta$ -unsaturated carboxylic acid with trichlorogermane, were unique in their chemical structures<sup>3</sup>, showed antitumor activity<sup>4</sup> and were capable of functioning as inducers of interferon<sup>5</sup>.

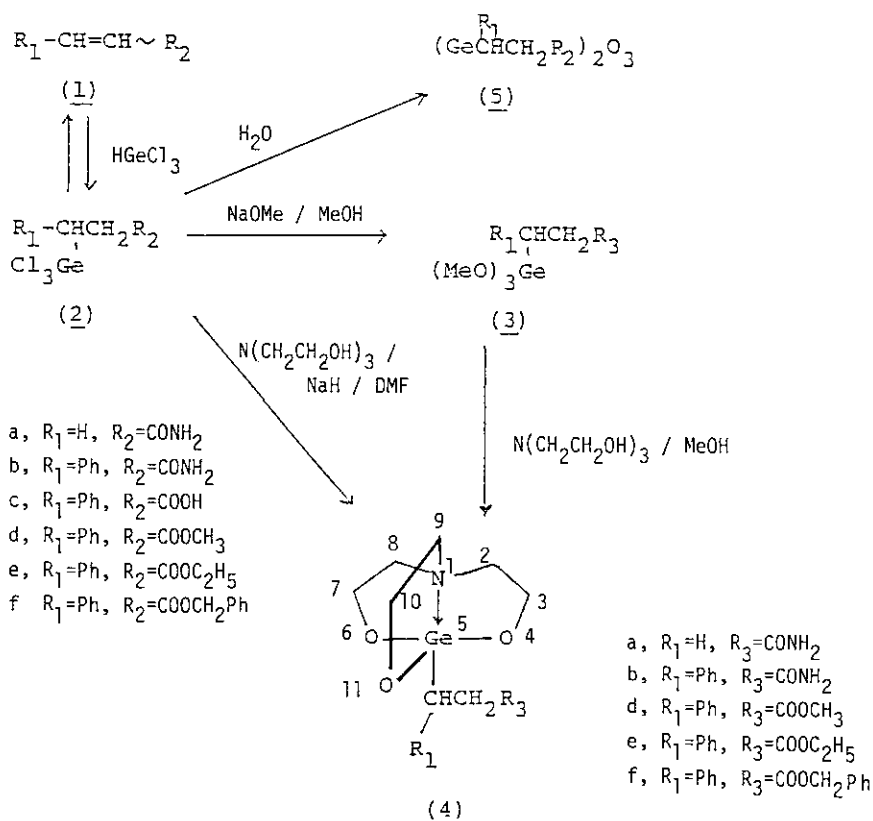
This report presents a direct general method for the synthesis of novel functionalized germatranes, which may be transformed to many other ones, by the nucleophilic displacement reaction of the trichloro group on (2) with triethanolamine instead of the process by hydrolysis, so as to compare with Ge-132 related compounds and silatranes<sup>6</sup> with respect to their physical and chemical properties, and bioactivities.

In a typical experiment (Method A), a mixture of (1a) (0.1 mol) and trichlorogermane (0.1 mol in 50 ml of dry ether) was stirred at 0-5°C (1h).

The corresponding germyl adduct (2a)<sup>7</sup> was obtained in 95% yield, mp 105°C. Subsequently (2a) (0.029 mol in 50 ml of abs. methanol) underwent methanolysis of the trichloro moiety by sodium methoxide (sodium (0.087 mol) in 100 ml of abs. methanol) to yield the corresponding trimethoxygermyl product (3a) which, without isolation, on refluxing in methanol with triethanolamine (0.029 mol, 6h) gave germatrane (4a)<sup>8</sup>, (62%) as white needles (chloroform), mp 177°C, m/z 292 (M<sup>+</sup>); ir (KBr): 3500, 3200(N-H), 1660, 1620 (CONH), 900 (Ge-O), 690 (Ge←N) cm<sup>-1</sup>; <sup>1</sup>H nmr [CD<sub>3</sub>OD]: 1.08 (2H, t, GeCH<sub>2</sub>), 2.38(2H, t, CH<sub>2</sub>CO), 2.91 (2H, t, NCH<sub>2</sub>), 3.75 (2H, t, CH<sub>2</sub>O). Similarity (2b) and (2d) twice underwent alcoholysis to give the corresponding product (4b) and (4d) in 70% and 61% yield, respectively. In the case of (2c) and (2e), however, on using methanol as the solvent, the ester (4d) was obtained in 4% and 47% yield, respectively. A similar reaction in (2d) afforded (4e) using ethanol instead of methanol. To avoid this disadvantageous procedure, a general synthetic method for germatrane derivatives was needed. For this purpose (4d) was obtained directly in one step in a 47% yield [mp and ir, and nmr spectra in agreement with (4d) obtained by Method A], when a solution of triethanolamine (0.01 mol) and 50% sodium hydride (0.06 mol) in dimethylformamide was added to a mixture of (1d) (0.01 mol) and trichlorogermene (0.01 mol in 30 ml of dry dimethylformamide) followed by refluxing for 6h (Method B). This method provided (4d) directly without the need for isolating (2d). Similarly, the corresponding germatranes (4a, b, e, and f) were obtained in 35%-66% overall yields (Method B) (Table I). But in the case of (2) obtained from (1) having a strong electron inductive group as acrylonitrile and cinnamionitrile, the corresponding products (4) were not obtained but the starting materials (1) could be recovered quantitatively. The formation of (1) may be considered to result from the elimination of trichlorogermene by the preferred triethanolamine, owing to the strong active proton at α-position on (2).

The <sup>1</sup>H nmr spectra of (4) showed interesting behaviour due to the effects of the germyl group, as in the case of sesquioxides<sup>9</sup>. That is, the germatrane framework in (4a) caused a significant upfield shift of the β proton on the carbamoylethyl group by 0.55 ppm and a downfield shift of the α proton by 0.20 ppm more than the chemical shifts of those of n-butylamide. Compared to those of triethanolamine, both protons of the NCH<sub>2</sub> and OCH<sub>2</sub> groups shifted downfield by 0.27 ppm and 0.17 ppm due to the effect of N<sup>δ+</sup>.

The mass spectra generally showed typical strong peaks of  $M^+-X$ ,  $M^+-X-CH_2O$ ,  $M^+-X-2CH_2O$ ,  $M^+-X-3CH_2O$  ( $X=R^1CHCH_2R^3$ ) besides those of the molecular ion  $M^+$ . DTA showed two endothermic peaks at  $68^\circ C$  and  $177^\circ C$ . The former peak may be considered due to cleavage of the  $N \rightarrow Ge$  bond. The coordination bond is also supported in the presence of the absorption<sup>10</sup> of  $690\text{ cm}^{-1}$  by ir spectrum. Investigation of the biological activities of these newly prepared compounds (4) is now being carried out.



Scheme

Table I. Preparation of the 5-substituted germatranes (4)

Unsaturated compound ( <u>1</u> )	Product ( <u>4</u> )	Yield(%) <sup>a</sup>	Mp °C
( <u>1a</u> )	( <u>4a</u> )	62 <sup>b</sup> , 66 <sup>c</sup>	177
( <u>1b</u> )	( <u>4b</u> )	70 <sup>b</sup> , 35 <sup>c</sup>	228
( <u>1c</u> )	( <u>4d</u> )	4 <sup>b</sup>	178
( <u>1d</u> )	( <u>4d</u> )	61 <sup>b</sup> , 47 <sup>c</sup>	178
( <u>1e</u> )	( <u>4e</u> )	47 <sup>b</sup> , 41 <sup>c</sup>	163
( <u>1f</u> )	( <u>4f</u> )	44 <sup>c</sup>	112

<sup>a</sup> Yield of pure isolated product.

<sup>b</sup> Yield from the corresponding germyl adducts (Method A).

<sup>c</sup> Method B.

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