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1-Acyloxygermatranes

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Abstract—A one-step method for the synthesis of 1-acyloxygermatranes $RC(O)OGe(OCH_2CH_2)_3N$ in the reaction of germanium dioxide with triethanolamine and a carboxylic acid was developed. 1- Acyloxygermatranes, including those containing biologically active acyloxy groups (R = $2\text{-}MeC_6H_4CH_2OCH_2$, C_6H_5, $2\text{-}HOC_6H_4$), were obtained with a 82–96.5% yield.

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Continuing interest in the 1-substituted germatranes is due to their specific biological activity [1, 2] unlike that of the corresponding silatranes [3]. Markedly greater stability of the germatrane ring to hydrolytic cleavage compared to silatrane allows using germatranes for transporting the biologically active fragments to the living cells [4–6].

The first specimen of 1-acyloxygermatranes, the 1-acetoxygermatrane $CH_3C(O)OGe(OCH_2CH_2)_3N$ was obtained in 91% yield by the reaction of 1-methoxygermatrane with 98% acetic acid or acetic anhydride in *o*-dichlorobenzene at 100°C [7].

We have developed a simple and convenient method for the synthesis of 1-acyloxygermatranes from germanium dioxide, triethanolamine, and a carboxylic acid in xylene or isoamyl alcohol.

$$GeO_2 + (HOCH_2CH_2)_3N \longrightarrow H_2O \cdot HOGe(OCH_2CH_2)_3N \xrightarrow[-2H_2O]{+\,RC(O)OH} \underset{\textbf{I–IV}}{RC(O)OGe(OCH_2CH_2)_3N}$$

R = CH_3 (**I**), $2\text{-}CH_3C_6H_4OCH_2$ (**II**), C_6H_5 (**III**), $2\text{-}HOC_6H_4$ (**IV**).

The reaction is performed by successive addition of water and a solution of a carboxylic acid in xylene or isoamyl alcohol to a mixture of stoichiometric amounts of germanium dioxide and triethanolamine.

The 1-germatranol hydrate [8, 9] formed in the first stage in the presence of water undergoes esterification with the carboxylic acid while the theoretical amount of hydration and formed water is distilled off, to afford the corresponding 1-acyloxygermatrane. The yield of compounds **I–IV** is 82–96.5%.

We have previously reported that the germatranol 1-hydrate when heated with an excess aliphatic alcohol is converted almost quantitatively to the corresponding 1-alkoxygermatrane [10]. It is noteworthy that in isoamyl alcohol (instead of xylene) the reaction with benzoic acid leads to 1-benzyloxygermatrane (**III**), but not the 1-isoamyloxygermatrane, and the reaction time is significantly reduced judging from the rate of release of the theoretical amount of water (Table 1).

The composition and structure of the synthesized 1-acyloxygermatranes was established by elemental analysis (Table 1), ^{1}H NMR (Table 2), and IR spectroscopy. The IR spectra of compounds **I–IV** contain the following absorption bands, cm^{-1}: ν_{GeOC}, ν_{COC} (1000–1010, 1020–1060, 1080–1110), and $\nu_{C=O}$ (1640–1680). The band of the stretching vibrations of OH group in **IV** appears at 3240 cm^{-1}.

EXPERIMENTAL

The melting points, yields, solvents, reaction time, and the elemental analyses data of the 1-acyloxygermatranes are given in Table 1. The ^{1}H NMR spectra

Table 1. Yields, melting points, and elemental analysis data of 1-acyloxygermatranes

Comp. no.	Reaction time, h	Yield, %	mp, °C (solvent)	Found, %				Formula	Calculated, %			
				C	H	Ge	N		C	H	Ge	N
I	3	94.2	210–216 (xylene)	34.95	5.35	25.83	4.86	$C_8H_{15}GeNO_5$	34.59	5.44	26.13	5.04
II	4	94.3	183–184 (xylene)	47.11	5.78	19.16	3.65	$C_{15}H_{21}GeNO_6$	46.93	5.51	18.91	3.65
III	8 1	96.5 82.0	258–262 (xylene) 257–262 (isoamyl alcohol)	46.04	5.19	20.56	4.80	$C_{13}H_{17}GeNO_5$	45.94	5.04	21.36	4.12
IV	3	94.7	225–226 (xylene)	44.57	4.65	20.53	4.06	$C_{13}H_{17}GeNO_6$	43.88	4.82	20.40	3.94

Table 2. ^{1}H NMR spectra of 1-acyloxygermatranes $RC(O)OGe(OCH_2CH_2)_3N$

Comp. no.	R	Solvent	δ, ppm (*J*, Hz)		
			OCH_2	NCH_2	R
I	CH_3	$CDCl_3$ $(CD_3)_2SO$	3.95 t ($^3J_{HH}$ 5.4) 3.62 t ($^3J_{HH}$ 5.6)	2.99 t ($^3J_{HH}$ 5.6) 2.82 t ($^3J_{HH}$ 5.4)	2.06 s 1.90 s
II	$CH_3C_6H_4OCH_2$	CD_3OD	3.87 t ($^3J_{HH}$ 5.6)	3.02 t ($^3J_{HH}$ 5.4)	2.29 (s, CH_3), 4.71 (s, CH_2), 6.86–7.18 m (C_6H_4)
III	C_6H_5	CD_3OD	3.85 t ($^3J_{HH}$ 5.6)	3.01 t ($^3J_{HH}$ 5.6)	7.57–8.00 m (C_6H_5)
IV	2-HOC_6H_4	CD_3OD	3.86 t ($^3J_{HH}$ 5.5)	3.00 t ($^3J_{HH}$ 5.6)	4.50 (s, OH), 6.91–6.99 m (C_6H_4)

were recorded on Bruker-400 spectrometer with an operating frequency 400 MHz in solutions of deuterated solvents (Table 2), internal reference HMDS. The IR spectra were obtained on a Bruker VERTEX 70 instrument from the tablets with KBr.

Triethanolamine pure quality was additionally distilled in a vacuum, bp 162–163°C (2 mm Hg).

Glacial acetic acid pure quality was distilled at atmospheric pressure. Germanium dioxide, benzoic acid, *o*-methylphenoxyacetic and salicylic acids of pure grade were used without additional purification.

General procedure for the synthesis of 1-acyloxygermatranes I–IV. A mixture of 0.01 mol of germanium dioxide, 0.01 mol of triethanolamine, and 1 ml of water was stirred for 5 min until 1-germatranol hydrate formed (solidification of the reaction mixture), and then a solution of 0.01 mol of a carboxylic acid in 200 ml of xylene or isoamyl alcohol was poured and the mixture was heated with a Dean–Stark trap until the theoretical amount of water was released. The hot solution was filtered, the small colorless crystals of 1-acyloxygermatrane precipitated at cooling to 20°C were filtered off, washed with diethyl ether, and dried in a desiccator in a vacuum of 15–20 mm Hg. The mother liquor was evaporated to two-thirds of volume and cooled to 20°C. The crystalline precipitate of 1-acyloxygermatrane was treated similarly to that precipitated of the solution directly after synthesis.

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