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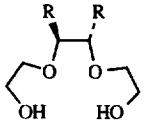
Substituted Triethylene Glycols From Dibutylstannylene Acetals

Gayane Godjoian, Vivian R. Wang, Alfredo M. Ayala, Ruben V. Martínez, Rolando Martínez-Bernhardt and Carlos G. Gutiérrez*

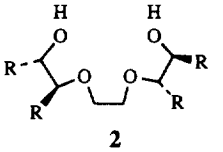
Department of Chemistry and Biochemistry, California State University, Los Angeles CA 90032-8202

Abstract : Stannylene acetals prepared from disubstituted vicinal diols can be alkylated with a half equivalent of 1,2-dibromoethane to produce tetrasubstituted triethylene glycols **2**, or with two equivalents of 2-chloroethanol to produce disubstituted triethylene glycols **1**.

Substituted triethylene glycols **1** and **2** are of considerable interest as components for incorporation into 18-crown-6 derivatives bearing a variety of structural or functional groups.[1] Disubstituted triethylene glycols **1** have been prepared by others by dialkylation of disubstituted ethylene glycols with (for example) ethyl diazoacetate/BF_3·Et_2O, with subsequent reduction of the resulting diester to the diol.[2] In those cases where substituents R are sensitive to reduction, the dialkylation has been accomplished with protected haloethanols and base.[3] The preparation of tetrasubstituted triethylene glycols **2** is less direct. Synthesis has required the extensive use of protective groups; the protection/deprotection steps frequently outnumber those which construct the triethylene glycol backbone.[1,3]



1

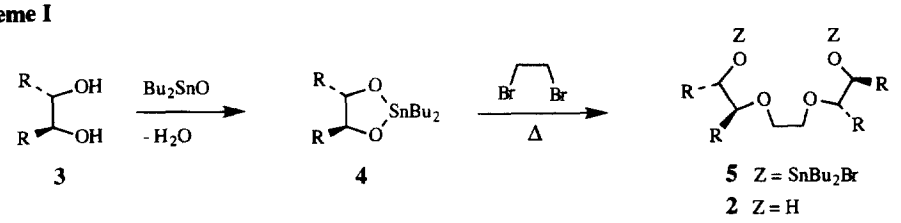


2

We report here that both types of these triethylene glycols may be prepared more directly from organotin derivatives of substituted ethylene glycols. Organotin alkoxides are useful synthetic intermediates in that the oxygen is more nucleophilic and less basic than in the parent alcohol.[4] Stannylene acetals (from the reaction of dialkyltin oxides and diols) have been used primarily in carbohydrate chemistry to effect selective alkylation of particular hydroxyls in molecules wherein several are present.[5] Also, it has been reported that while acylation of both Sn-O bonds is common,[6] alkylation is generally limited to mono-, and then with activated alkyl (benzyl, allyl, methyl) halides.[4,7]

We have found that 2,2-dibutyl-2-stanna-1,3-dioxolanes **4** can be monoalkylated with 1,2-dibromoethane to acyclic products **5**, which are subsequently destannylated to the tetrasubstituted triethylene glycols **2, Scheme I**. For example, a neat mix of two equivalents of **4a** (R= CH_2OCH_2Ph) (prepared in 92% yield from (*S,S*)-2,3-di(benzyloxymethyl)ethanediol[8] and dibutyltin oxide in toluene, with azeotropic removal of water) and one equivalent of ethylene bromide was heated at 110° for 12h to result in the alkylation of one Sn-O in each stannylene acetal to produce the bis(dibutylbromostannyl) dialkoxide **5a** (R= $SnBu_2Br$).[9] This was destannylated by passage through a column of silica gel, and (2*S*, 3*S*, 8*S*,9*S*)-1,9-dibenzyloxy-3,8-di(benzyloxymethyl)-4,7-dioxadecane-2,9-diol (**2a**) was isolated in 71% yield. The destannylation can be accomplished alternatively by reaction of the intermediate bis(dibutylhalotin alkoxide) **5** with oxalic acid.[10]

Scheme I



ethylene glycol **3** R		stannylene acetal **4** yield	mp	triethylene glycol **2**[d] yield[e]	^{1}H NMR[f]
3a	CH_2OCH_2Ph[a]	**4a** 90%	93.5-95°	**2a** 71%	δ = 3.2-3.9 (m, 18H), 4.42 (m, 8H), 7.20 (s, 20H)
3b	CO_2CH_3	**4b** 95%	180-181°[b]	**2b** 82%	δ = 3.75(overlapping singlets, 16H), 4.55 (s, 4H), 4.51 (s, 2H)
3c	CH_3	**4c** 92%	134°[c]	**2c** 5%	δ = 1.07 (d, J=4.5Hz, 12H), 2.94 (br s, 2H), 3.2-3.9 (m, 8H)

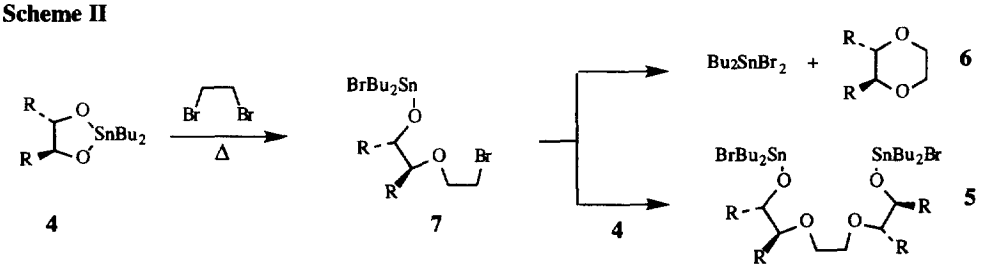
[a]Reference 8. [b]Reference 7. [c]Reference 11. [d]Elemental analyses of new compounds were consistent with assigned structures. [e]After destannylation of intermediates **5** on silica gel or with oxalic acid. [f]$CDCl_3$ with TMS internal standard.

Noteworthy is the preparation of tetra(carboxymethyl)triethylene glycol **2b** from (*R,R*) dimethyl tartrate (**3b**) in an overall 78% yield. While the preparation of triethylene glycols having a similar substitution pattern have been reported, the present method avoids the many protection/deprotection steps, and the use of toxic thallium alkoxides to effect alkylation.[3a] Indeed, the organotin approach we describe here avoids the use of any external base.

Surprisingly, the reaction of dimethyl stannylene acetal **4c** and 1,2-dibromoethane produced 2,3-dimethyl-1,4-dioxane[12] as the major product, and after destannylation of the non-volatile residue, also (2*S*, 3*S*, 8*S*, 9*S*)-3,8-dimethyl-4,7-dioxadecane-2,9-diol (**2c**) but in a disappointingly low 5% yield [based on (*S,S*)-2,3-butanediol]. This product was identical to a sample prepared by the $BH_2Cl{\cdot}SMe_2$ reduction of the glyoxal bisacetal of (*S,S*)-2,3-butanediol.[13]

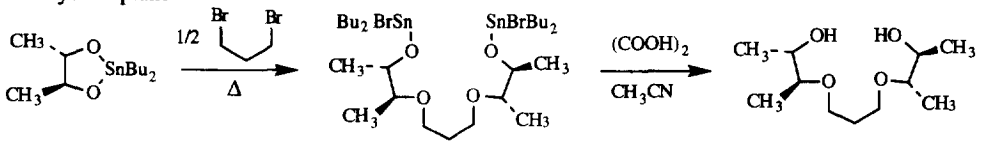
The reactions appear to follow the outline in **Scheme II**, with the product composition determined by the competition for intermediate **7** by either the second equivalent of **4** to produce **5**; or by internal alkylation to produce dioxanes **6**. While monoalkylation of **4** is generally observed, internal dialkylation to produce the dioxane **6** is possible and appears dependent on the nature of the substituents R. The scope of the reaction of stannylene acetals **4** with dihaloethanes is currently under investigation by variation of the R groups.

Scheme II



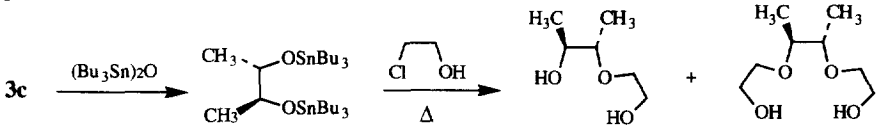
The dialkylation of the stannylene acetals **4** may also be limited to the formation of six-membered rings. The use of 1,3-dibromopropane resulted only in monoalkylation of 2 equivalents of stannylene acetal **4c** to produce (2*S*, 3*S*, 9*S*, 10*S*)-3,9-dimethyl-4,8-dioxaundecane-2,10-diol (**9**) (after destannylation of intermediate **8** with oxalic acid), a homolog of **2c** bearing an additional methylene group [and identical to the product reported from the BH_2Cl reduction of the malonaldehyde bisacetal

produced from (*R,R*)-2,3-butanediol].[13] We detected no corresponding 2,3-dimethyl-1,4-dioxacycloheptane.



4c **8** **9**

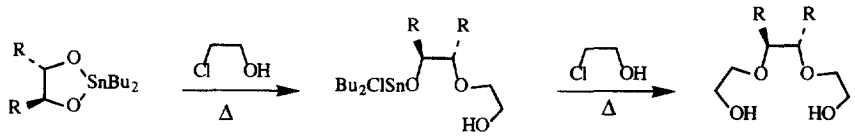
The use of organotin intermediates also suggested an alternative synthesis of disubstituted triethylene glycols **1**. Bistributylstannyl ether **10**[12b] was prepared [from **3c** and bis(tributyltin)oxide] with the intent of dialkylating it with two equivalents of 2-chloroethanol to produce the dimethyltriethyleneglycol **1a** (R= CH_3). However, the reaction product consisted of a 42% yield of a mixture of **1c** and dimethyldiethylene glycol **11** (the product of monoalkylation). The remainder of the chloroethanol was presumably lost as ethylene oxide by a competing process which requires initial exchange of a tributylstannyl group from **10** to chloroethanol, and subsequent internal alkylation[14] of that intermediate to generate the epoxide and tributyltin chloride. This result was not unexpected in that tributyltin ethers are prone to exchange among oxygen nucleophiles, and also hydrolyze slowly with atmospheric moisture.



10 **11** **1c**

However, stannylene acetals **4** can be sequentially dialkylated[15] with 2-chloroethanol without solvent, **Scheme III**. For example, at 140 °C we observed clean monoalkylation, even with excess cloroethanol, of **4c** (R= CH_3) to (*4S, 5S*)-4-methyl-3-oxa-1,5-hexanediol **11** [^{1}H NMR δ= 1.03 (d, J= 6 Hz), 3.0-3.8 (m, 6H), 4.3 (br s, 2H)] in 93% yield after destannylation of the intermediate chlorodibutyltin alkoxide (**12c,** R=CH_3) on silica gel. However, at 170 °C we observed dialkylation of **4c** to (*4S,5S*)-4,5-dimethyl-3,6-dioxa-1,8-octanediol (**1c**) in 84% yield. While the diacylation of stannylene acetals is well documented,[6] this report shows that dialkylation with monohalogen compounds is also possible, and synthetically useful. The second Sn-O bond of stannylene acetals is not inert towards alkylation, but considerably less reactive than the first . Earlier reports describe the solution chemistry of stannylene acetals, and the sequential dialkylation of Sn-O bonds in stannylene acetals with monohalides is rarely observed, possibly because the reaction temperature was limited by the solvent.[16]

Scheme III



4 **12** **1**

stannylene acetal **4** R		triethylene glycol **1**[a] yield		^{1}H NMR[b]
4a	CH_2OCH_2Ph	**1a**	80%	δ = 3.60 (broad m, 16H), 4.47 (d, 4H), 7.25 (s, 10H)
4b	CO_2CH_3	**1b**	78%	δ = 3.3-5.0 (m including broad singlet at 3.65, 18H)
4c	CH_3	**1c**[c]	84%	δ = 1.06 (d, 6H, J=6 Hz), 3.65 (m, 10H), 3.96 (s, 2H)

[a]Elemental analyses of new compounds were consistent with assigned structures. [b]$CDCl_3$ with TMS internal standard. [c]Reference 2.

We are currently investigating the incorporation of fragments **1** and **2** into crown ethers.

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