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NOVEL INSERTION REACTIONS INTO CYCLIC TIN—OXYGEN COMPOUNDS

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Summary

A series of novel insertion reactions of cyclic carbonyl compounds into cyclic tin—oxygen compounds is described. Cyclic carboxycarbonate (**1**) and isatoic anhydride (**4**) react with cyclic stannoxane (**2**) to give the acyclic diester (**3**) and diamide (**5**) respectively. Cyclic anhydrides derived from aspartic and glutamic acids (**6**, **7**, **10** and **11**) react with **2** to give the macrocyclic tetralactones (**8**) and (**9**), and dilactones (**12**) and (**13**) respectively. These reactions may be of general synthetic value because of their high specificity. They lead either to singly acylated, acyclic products (**3** and **5**), or to regiospecific macrocyclic products (**8**, **9**, **12** and **13**) in preference to oligomers. The high specificity of these reactions is attributed to: (i) the dual function of the tin element, which may act either as activating group or as protecting group, and (ii) the occurrence of non-covalent transannular interactions between tin and oxygen in the cyclic stannoxane **2**.

Introduction

The chemical versatility of organotin derivatives [1—4] encouraged us to use these compounds as covalent templates for organic synthesis. In this approach, difunctional organic substrates are treated with difunctional tin compounds to give cyclic derivatives which can be regarded as tin templates.

The interdependance of the functional groups in these templates made their selective mono-derivatization possible [5], while their defined geometry allowed their efficient conversion to macrocyclic products in preference to polymeric materials [6].

Further expansion of the method seemed promising, but highly dependent on the development of additional condensation reactions and on a better understanding of the factors governing the chemical reactivity of organotin derivatives towards organic substrates. In an attempt to overcome this gap, we decided to examine the chemical behavior of cyclic tin—oxygen compounds

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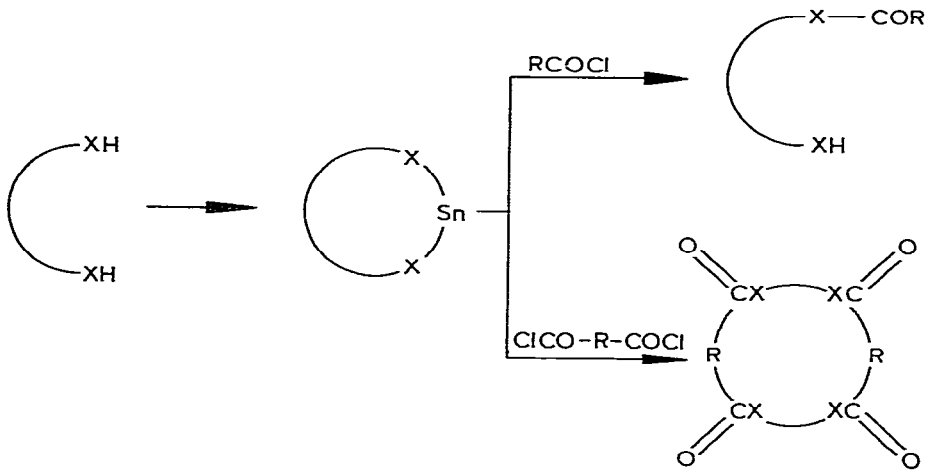
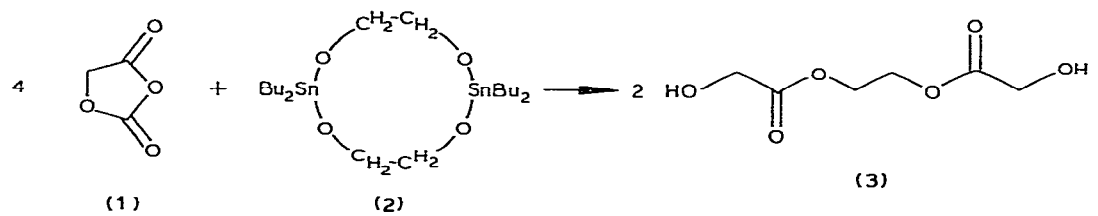
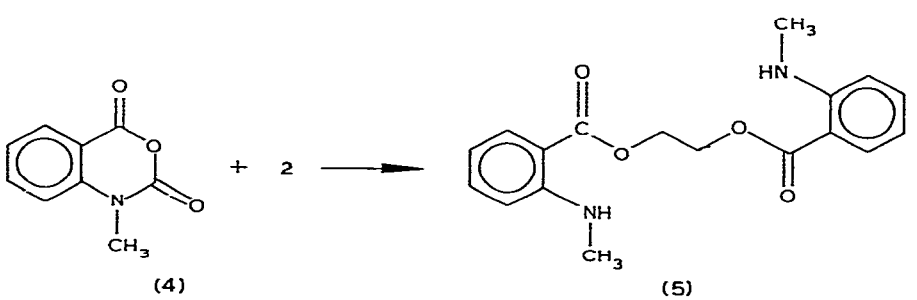


towards activated, cyclic, organic carbonyl derivatives. In this paper we describe the reactions of cyclic distannoxanes with (i) cyclic carboxy-carbonates, (ii) isatoic anhydride, and (iii) cyclic anhydrides, and demonstrate the pronounced specificity of some of these reactions.

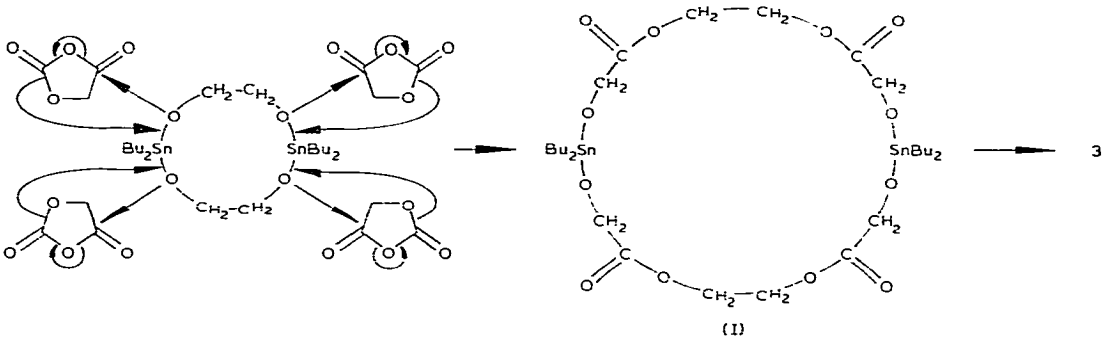
Results and discussion

The first reactions investigated were the reactions of distannoxane **2** with carboxy-carbonates and isatoic anhydride. Cyclic carboxy-carbonates and isatoic anhydride contain active carbonyl groups, as is evident from their IR absorptions at 1880 and 1820 cm^{-1}, and 1760 and 1700 cm^{-1}, respectively. The cyclic carboxy-carbonate derived from glycolic acid was chosen as the organic substrate, **(1)** [7], and the cyclic distannoxane **2** as the tin component, and rapid reaction between these compounds gave the hydroxy ester **3** in 80% yield. Similarly, treatment of isatoic anhydride **4** with distannoxane **2** gave the corresponding anthranilic ester **5** in 45% yield.





These reactions may be regarded as occurring via nucleophilic attack of the stannoxane on the anhydride with concurrent opening of the ring species. Subsequent loss of carbon dioxide and combination of the two reactants then leads to intermediates of type I, which provide the acylated products after hydrolytic cleavage.

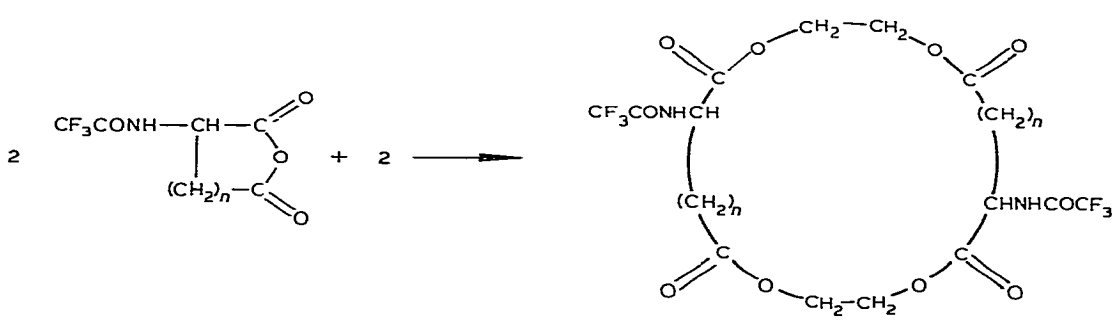


(I)

These reactions permit esterification of alcohol groups with either a single hydroxy acid or amino acid without competing oligomerization of the acylating agents. This controlled acylation can be attributed to the reduced reactivity of the intermediate I towards electrophiles compared with that of the starting material **2**.

The two acylating agents considered above undergo decarboxylation during the insertion. They thus retain only one active carbonyl group and convert diols into linear acylated products. Cyclic dicarbonyl derivatives which would not undergo decarboxylation and retain two active carbonyl groups were expected to be suitable for the preparation of macrocyclic products, since such compounds could interlink two diol residues to a ring product. This expection was realized with five- and six-membered cyclic anhydrides derived from aspartic and glutamic acid respectively.

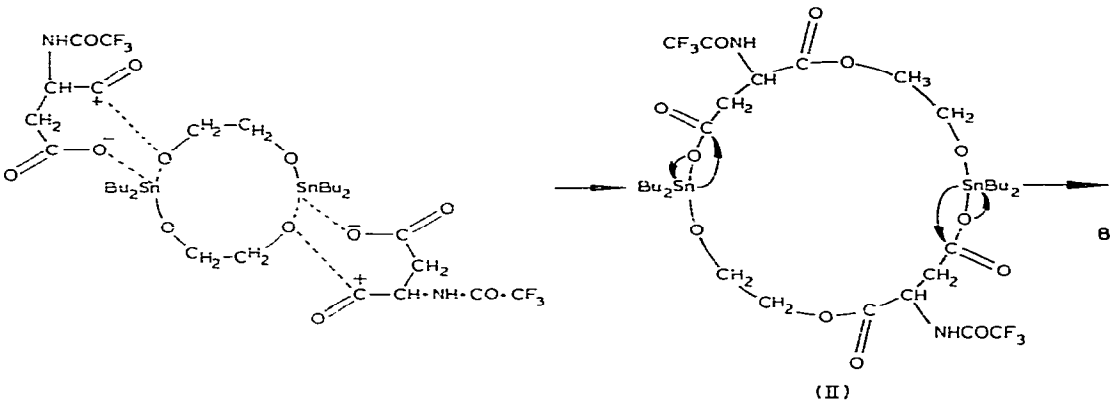
As indicated by their IR spectra, (IR absorptions at 1820 and 1770 cm^{-1}), these compounds also contain activated carbonyl groups. Treatment of trifluoroacetyl aspartic acid anhydride (**6**) or of trifluoroacetyl glutamic acid anhydride (**7**) with distannoxane (**2**) provided the macrocyclic tetralactones (**8** and **9**, respectively) in 70% and 49% yield [8].



(6, $n = 1$; 7, $n = 2$)

(8, $n = 1$; 9, $n = 2$)

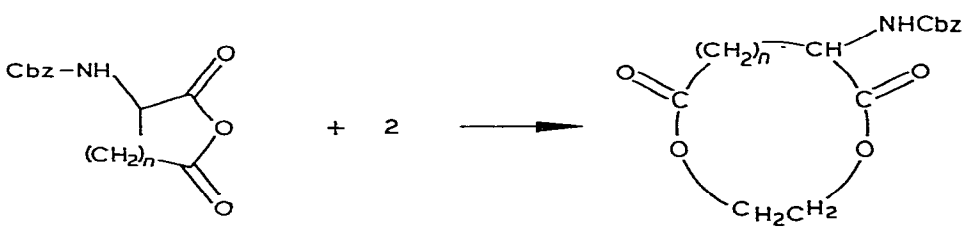
This reaction may be thought of as occurring by attack of two anhydride molecules at the most distant positions at the cyclic distannoxane **2** to give an intermediate II. The latter then releases the observed products with concurrent loss of dibutyl tin oxide. The regiospecific attack of the anhydride molecules at the most distant positions may be attributed to some non-covalent transannular



(II)

interactions between tin and oxygen in the distannoxane **2**. Such interactions may modify the relative reactivity of the two diagonal tin—oxygen bonds and thereby cause preferential attack on either of the two bonds and formation of one product. Non-covalent interactions between four coordinated tin derivatives and oxygen donors with simultaneous expansion of the coordination number from four to five are well documented [9]. As for the loss of dibutyl tin oxide, expulsion of dibutyl tin oxide was recently suggested to occur in related condensation reactions [10].

It was of interest to see whether modification of the anhydride would effect the reaction pathway. To this end the reactions of the less activated carbobenzoxy derivatives of aspartic and glumatic acid anhydride with distannoxane **2** were investigated. Treatment of distannoxane **2** with carbobenzoxy anhydrides **10** or **11** gave the macrocyclic dilactones **12** and **13**, respectively, in rather low yields, instead of the expected tetralactones.

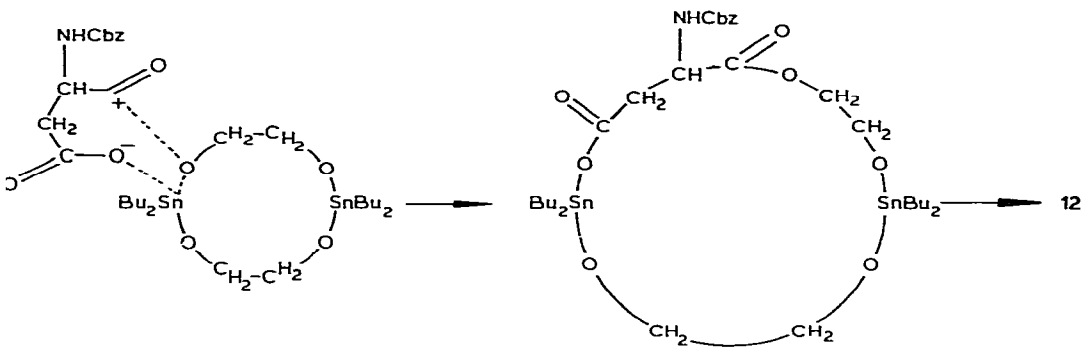


(**10**, $n = 1$; **11**, $n = 2$)

(**12**, $n = 1$; **13**, $n = 2$)

The formation of the macrocyclic dicarbonyl compounds may be explained in terms of attack of a single anhydride molecule at the distannoxane **2** and subsequent expulsion of the macrocyclic product and dibutyl tin oxide.

The different products obtained from the trifluoroacetyl derivatives **6** and **7** and the carbobenzoxy derivatives **10** and **11** may be attributed to the higher



(III)

reactivity of the former. While in the former case two anhydride molecules do insert prior to thermal expulsion of the product, in the latter case only one molecule inserts prior to competitive thermal cleavage, to give the macrocyclic dilactones **12** and **13**.

Conclusion

We have demonstrated that the cyclic distannoxane **2** reacts with cyclic dicarbonyl derivatives to give either linear or cyclic products. The outcome of these reactions is highly dependent on the reactivity of the organic substrate. Highly reactive substrates can insert into each of the four tin—oxygen bonds (for example carboxy carbonate or isatoic anhydride) to give acyclic products. Less reactive substrates such as cyclic anhydrides can insert only into two tin—oxygen bonds (transannular located tin—oxygen bonds), or into a single tin—oxygen bond before competitive thermal processes occur, to give macrocyclic products. Due to the interdependence of the four tin—oxygen bonds in the distannoxane **2**, (geminal interactions and transannular, non-covalent interactions), these reactions are characterized by pronounced selectivity and enable regiospecific preparation of macrocyclic compounds.

Experimental

*Reaction of cyclic anhydrocarboxyglycolic acid (**1**) with distannoxane (**2**)*

A solution of anhydride (**1**) 11 g (0.05 mol), and distannoxane (**2**) 2.36 g (0.004 mol) in 250 ml of dry chloroform was heated under reflux with exclusion of moisture for 4 h. Concentration of the mixture and chromatography of the residue on silica gel gave 1.16 g (0.0065 mol, 81%) of the hydroxy ester (**3**) as colourless oil. IR (Nujol), ν 3500 and 1750 cm^{-1}: NMR ($CDCl_3$), δ 4.78 (d, J 9.5 Hz, 4H), 4.41 (s, 4H) and 4.35 ppm (d, J 9.5 Hz, 2H): mass spectrum m/e = 178 (molecular ion peak).

*Reaction of isatoic anhydride (**4**) with distannoxane (**2**)*

A solution of 1.77 g (0.01 mol) of isatoic anhydride (**4**) in 100 ml of dry chloroform was added dropwise to a boiling solution of 2.92 g (0.005 mol) distannoxane (**2**) in 250 ml of dry chloroform. After the addition reflux was

continued for 3 h and the mixture concentrated in vacuo. Chromatography of the residue on silica gel gave 736 mg (0.00225 mol, 45%) of the anthranilide (5) m.p. 155—157°C. IR (Nujol), ν 3370, 1630, 1570, 1250, 1230, 1170, 1160 and 1030 cm^{-1}: NMR ($CDCl_3$) δ, 7.8 (d, 1H), 7.3 (m, 2H), 6.4 (d, 2H), 4.4 (s, 2H) and 2.95 ppm (2s, 3H): mass spectrum m/e = 328 (molecular ion peak).

*Reaction of anhydrides (***6***,* **7***,* **10** *and* **11***) with distannoxane (***2***)*

A solution of 1.46 g (0.0025 mol) stannoxane **2** and 1.125 g (0.005 mol) *L*-trifluoroacetyl glutamic anhydride **7** in 150 ml of dry chloroform was heated under reflux for 2 h. The mixture was then concentrated in vacuo and chromatographed on silica gel (Silicagel 60, Merck). Elution with mixtures of benzene and ethylacetate yielded 669 mg (0.00124 mol, 49%) of the macrocyclic tetralactone **9**. The aspartic acid derivatives **6** and **10** and the glutamic acid derivative **11** were treated with stannoxane **2** by analoguous procedures to provide the macrocyclic tetralactone **8**, and the macrocyclic dilactones **13** and **12** in 70, 10 and 35% yields, respectively. The macrocyclic compounds exhibited the following spectral properties: Tetralactone **8**: IR (Nujol), ν 3300, 1720, and 1550 cm^{-1}: NMR (CD_3OD), δ 4.48 (m, 1H), 3.8 (t, *J* 5 Hz, 2H), 3.32 (t, *J* 5 Hz, 2H), 2.46 (dd, *J* 17 and 8 Hz, 1H) and 2.58 ppm (dd, *J* 17 and 5 Hz, 1H): mass spectrum m/e = 510 (molecular peak): Tetralactone **9**: IR (Nujol), ν 3300, 1750 and 1705 cm^{-1}: NMR (DMSO), δ 4.5 (m, 1H), 4.18 (m, 2H), 3.68 (t, *J* 5 Hz, 2H), 2.43 (t, *J* 7 Hz, 2H), 2.2 (m, 1H) and 2.04 ppm (m, 1H): mass spectrum m/e = 270 (molecular peak/2 + 1): Dilactone **12**: m.p. 112°C: IR (Nujol), ν 3400, 3320, 1740, 1685 and 1535 cm^{-1}: NMR (DMSO), δ 7.78 (d, *J* 7.9 Hz, 1H), 7.35 (s, 5H), 5.04 (s, 2H), 4.41 (m, 1H), 4.05 (t, *J* 5.3 Hz, 2H) 3.53 (t, *J* 5.3 Hz, 2H) and 2.64 ppm (m, 2H): mass spectrum m/e = 293 (molecular ion): Dilactone **13**: IR (Nujol), ν 3320 and 1710 cm^{-1}: NMR (DMSO), δ 7.735 (d, *J* 9 Hz, 1H), 7.36 (s, 5H), 5.04 (s, 2H), 4.07 (m, 3H), 3.57 (t, 2H), 2.32 (t, 2H), 1.95 (m, 1H) and 1.79 ppm (m, 1H): mass spectrum m/e = 307 (molecular ion peak).

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