COMMUNICATIONS

LETTERS

Reinvestigation of Chlorination of Saccharin. A mild and convenient Synthesis of *o*-Cyanophenylsulfonyl Chloride

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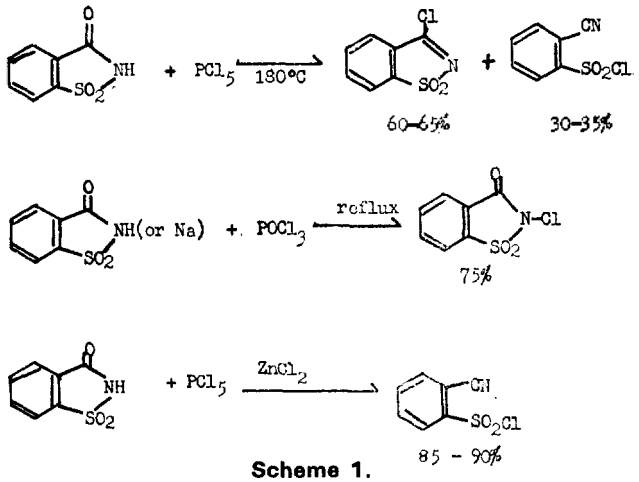
In a previous paper[1], we had described the synthesis of some pivotal saccharin derivatives as the potential agrochemicals and antiinflammatory agents from pseudosaccharin chloride, and also studied the chlorination of saccharin.

The present paper reports the results of a study of the chlorination of saccharin. We carried out the chlorination of saccharin using Jesurun's procedure[2,3] and the modified methods[4,5]. In the case of the chlorination of saccharin with phosphorous pentachloride at 180°C, the product obtained always resulted in a mixture of 3-chloro-1,2-benzisothiazole-1, 1-dioxide (pseudosaccharin chloride) and *o*-cyanophenylsulfonyl chloride as an impurity. Separation by preparative TLC on Silica gel plate gave 60-65 % of pseudosaccharin chloride and 30-35 % of *o*-cyanophenylsulfonyl chloride, respectively.

According to Yoon[6], *o*-cyanophenylsulfonyl chloride has been shown to be high antifungal activity against a certain fungus. Therefore, we have tried to prepare *o*-cyanophenylsulfonyl chloride from saccharin in a high yield under mild condition.

We have found that the use of phosphorous pentachloride and $ZnCl_2$ as a catalyst gave *o*-cyanophenylsulfonyl chloride in a comparable yield, whereas the use of $POCl_3$ results in only N-chlorosaccharin in 75 % yield instead of pseudosaccharin chloride or o-cyanophenylsulfonyl chloride. IR and mass spectrum of *o*-cyanophenylsulfonyl chloride show a sharp band at 2215cm^{-1} and a molecular ion peak at 201 m/e, respectively. ^{1}H-NMR spectrum of this compound also show the typical pattern of 1,2-disubstituted benzene at 7.8 - 8.2 ppm.

The standard procedure for preparing N-chlorosaccharin has been performed by passing chlorine gas through a cold aqueous solution of saccharin sodium salt[7,8]. Thus, N-chlorination of saccharin or its sodium salt with $POCl_3$ is considered to be a new procedure.



Scheme 1.

Cignarella and his co-worker[9] have synthesized *o*-cyanophenylsulfonyl chloride from dithiosalicylamide through two steps. However, our new procedure has an economical advantage and is also more convenient than Cignarella's method using dithiosalicylamide as the starting material.

On the other hand, the cleavage of the five-membered ring in saccharin and N-substituted derivatives by a nucleophilic reagent has been reported to occur at C-N bond on the five-membered ring[10-15]. However, treatment of saccharin with phosphorous pentachloride and $ZnCl_2$ as a catalyst gave *o*-cyanophenylsulfonyl chloride in good yield by the cleavage at S-N bond on the five-membered ring of saccharin.

Synthesis of o-cyanophenylsulfonyl Chloride. Mixture of saccharin(0.1 Vmole, 18.3g), PCl_5 (0.105 mole, 21.5 g) and a catalytic amount (0.2 - 0.3 g) of $ZnCl_2$ was heated at 65 - 70°C for 15 - 30min. After distillating $POCl_3$, the residue was cooled to room temperature and poured into 300 *ml* of cold water with stirring. The precipitate was filtered, washed with water and dried to give 17 - 18Vg(85 - 90 %) of *o*-

cyanophenylsulfonyl chloride. mp 62–63°C(lit[9]. mp 69–69.5°C)IR(nujol) 3090(aromatic C–H), 2215(CN), 1340, 1178 cm^{-1} (SO_2); ^{1}H-NMR($CDCl_3$)δ7.8 – 8.2 ppm(m, 4H); MS, m/e(relative intensity) 203(4, M+2), 202(2, M+1), 201 (11, M^+), 166(50), 102(100), 75(40).

Synthesis of N-chlorosaccharin. A mixture of saccharin (0.05 mole, 9.15g) or its sodium salt (0.05 mole, 20.5g) and $POCl_3$ (0.3 mole, 30m*l*) was refluxed for 2 – 3 h. After distillation of excess $POCl_3$, the residue was poured into 400 m*l* of cold water with stirring, filtered and dried to give 7.6g (75%) of N-chlorosaccharin. mp 216 – 217°C(lit[8,9]. mp 215 – 216°C); IR(nujol) 1680(C=O), 1565(aromatic C=C), 1305, 1150 cm^{-1} (SO_2); ^{1}H-NMR ($CDCl_3$)δ8.1 ppm(s, 4H).

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A Short Synthesis of Dendrolasin

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Dendrolasin(**1**) is a representative furanoid sesquiterpene isolated from insects and other sources[1]. Some syntheses of dendrolasin[2] start with 3-substituted furans as starting materials and involve classical problems of forming trans trisubstituted double bond common to many acyclic terpenes. Lithium di (3-furyl) cuprate was used to synthesize 3-substituted furans in general[3]. Geranylacetone[4] and myrcene[5] were also used in the synthesis of dendrolasin: in these cases, furan ring formation is the key step.

A biogenetic-type synthesis was accomplished in this laboratory using farnesol as the starting material[6]. The scheme involves Sharpless epoxidations of allylic and homoallylic alcohols and a crucial 3,4-epoxyaldehyde-furan conversion on a silica gel column. This report describes a new short synthesis of dendrolasin from methyl farnesoate(**2**) in which the homoallylic alcohol intermediate(**5**) is synthesized in three steps from **2**.

Methyl farnesoate(**2**) was dissolved in THF and added to 1.05 eq. of lithium cyclohexylisopropylamide in THF at −78°. The THF solution was stirred 20 minutes and 2.0 eq. of trimethylsilyl chloride was added to quench the enolate anion. After stirring 30 minutes, standard work-up provided almost quantitative yield of the silyl enol ether(**3**). The H-2 singlet at δ5.60 in the nmr spectrum of methyl farnesoate disappeared completely suggesting facile enolate and subsequent silyl enol ether formation. Under the reaction conditions employed, kinetically favored enolate anion should be predominantly produced and the structural assignment of **3** with an exo methylene unit is supported by the disappearance of the H-15 methyl singlet at δ2.15. Stereochemistry at C-1 involving $-OSiMe_3$ and $-OMe$ is more difficult to define and no effort was made to distinguish E-Z isomers of **3** since both should give rise to the same product at the next step.

Regeneration of methyl ester functionality resulted in the formation of varying ratios of α,β- and β,γ -unsaturated esters depending on the desilylation conditions used. When the silyl enol ether(**3**) was treated with tetra-n-butylammonium fluoride in THF at room temperature, methyl farnesoate was the major component of the product mixture. In the nmr spectrum, the characteristic peaks at δ5.60 and δ2.15 decreased relative to other signals, but the signals for the desired β,γ-unsaturated ester(**4**) were not clearly seen. The ratio of α,β- and β,γ-unsaturated esters was roughly calculated to be 7:3 from the nmr integration experiment.

Simple elution of **3** through a silica gel column with hexane-ethyl acetate(50:1 and 20:1) produced 85% yield of a product which turned out to be 35:65 mixture in favor of the deconjugated ester (**4**). New signals at δ3.04 for H-2 and at δ4.88