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Synthesis, characterization and the antifungal activity test of some organotin(IV) benzoates

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Abstract. In continuing search on the biological activity of the organotin compounds we are working with, We here reported the synthesis and the antifungal activity test of three organotin(IV) complexes of dibutyltin(IV) dibenzoate (**3**), diphenyltin(IV) dibenzoate (**6**) and triphenyltin(IV) benzoate (**9**). These three compounds were prepared by the reaction of dibutyltin(IV) dichloride (**1**), diphenyltin(IV) dichloride (**4**), and triphenyltin(IV) chloride (**7**) via dibutyltin(IV) oxide (**2**), diphenyltin(IV) oxide (**5**), and triphenyltin(IV) hydroxide (**8**) with benzoic acid. The product obtained in each step was characterized by UV, IR and NMR spectroscopies and also microelemental analysis. The antifungal activity test was carried out against *Fusarium oxysporum* strain. The results showed that the inhibition zone shown by these organotin(IV) benzoate were found by far much more active compared to the free benzoic acid, the starting materials **1**, **4**, **7**, and the intermediate products, **2**, **5** and **8**. The inhibition zone of each of the compounds tested was compared with the control where the fungus alone was grown in the media. The results showed that triphenyltin(IV) benzoate (**9**) was the most active compound against the fungus and the minimum inhibitory concentration obtained was about 0.7 mM.

Keywords: antifungal, organotin(IV) benzoate, minimum inhibitory concentration, synthesis

1. Introduction

Organotin(IV) compounds are characterized by having at least one direct covalent bond between Sn and C from the organic group. In this compounds, the center is Sn atom with tetravalent bonds and can be classified as mono-, di-, tri- and tetraorganotin(IV) depending on the number of alkyl (R) or aryl (Ar) groups attached directly to Sn. The anions can be in the form of chloride, iodide, fluoride, oxide and hydroxide ions [1]. Carboxylates have also been found to be effective as anions [2-10].

The interest in organotin(IV) compounds is not only due to the interesting feature in their chemical and structural properties [2, 11, 12], but also because of the growing use as agricultural biocide [1]; antifungal [1, 10], anticancer/anti-tumor agent [3-6], anticorrosion [7, 8], antimalarial [9, 13] and antimicrobial [14, 15].



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The application of organotin(IV) compounds in industry, agriculture and biology is increasing rapidly and is predicted to increase in the next few years. This is because organotin(IV) compounds are known as compounds that exhibit strong biological activity. Their compounds are very active in biological activities, even at very low concentrations [1]. The biological activities of organotin(IV) compounds are determined by the number and basic properties of the organic groups attached to the central Sn atom [1, 11]. The anion bound to Sn atom is a secondary determinant in the activity of the organotin(IV) compound.

In this work, the biological activity test as antifungal was carried out by the method of solid agar media against fungus of *Fusarium* (*Fusarium oxysporum*), which is known as a parasitic fungus.

2. Experimental

2.1. Materials and characterisation techniques

The materials used are chemical substances with pro analytical grade reagents consisting of: $(C_4H_9)_2SnCl_2$, $(C_6H_5)_2SnCl_2$, $(C_6H_5)_3SnCl$, NaOH, methanol, DMSO (dimethyl sulfoxide), benzoic acid and PDA (Potato Dextrose Agar) and used as received without purification.

The 1H and ^{13}C NMR spectra were measured using a Bruker AV 600 MHz NMR (600 MHz for 1H and 150 MHz for ^{13}C). The solvent used in the experiments was DMSO- D_6 and measured at 298K. The number of runs used for 1H experiments were 32 with reference at DMSO signal at 2.5 ppm, while the ^{13}C were 1000-4000 scans with the reference of DMSO signal at 39.5 ppm. The microelemental analysis (CHNS) was carried out using Fision EA 1108 series elemental analyser. The IR spectra were recorded with Bruker VERTEX 70 FT-IR spectrophotometer in the range $4000-400\text{cm}^{-1}$ and with KBr discs. The measurement of UV spectra was measured with a UV-Shimadzu UV-245 Spectrophotometer on UV region. The measurement was conducted in 1mL quartz-cells. Methanol was used as the solvent in the preparation of sample with concentration of 1.0×10^{-5} M.

2.2. Preparation of organotin(IV) benzoates

The preparation of the organotin(IV) benzoates was done using methods previously [5-10]. This procedure was adapted from the work by Szorcik *et al.* [12]. The procedure in the preparation of dibutyltin(IV) dibenzoate is as follows:

A mass of 3.0383 g (0.01 mol) $[(n-C_4H_9)_2SnCl_2]$ (**1**) in 50 mL methanol was added with 0.8 g (0.02 mol) NaOH. The reaction mixtures were stirred for about 60 minutes. Compound $[(n-C_4H_9)_2SnO]$ (**2**) was precipitated out as white solid, filtered off, washed successively with double distilled water and methanol (3 times) to dissolve any unreacted materials and dried *in vacuo*, the yield was 2.3508 g (95 %).

A mass of 0.374 g (1.5 mmol) compound **2** in 50 mL of methanol was added with 2 mole equivalents of benzoic acid and was refluxed for 4 hours at 60 – 62°C. After removal of the solvent by rotary evaporator, the compounds $[(n-C_4H_9)_2Sn(C_6H_5COO)_2]$ were washed successively with double distilled water and methanol to dissolve any unreacted materials, then dried *in vacuo* until they are ready for analysis and further use for biological test. The average yields were more than ~ 90 %.

A similar way was also used in the synthesis of diphenyltin(IV) dibenzoate $[(C_6H_5)_2Sn(C_6H_5COO)_2]$ (**6**) and triphenyltin(IV) benzoate $[(C_6H_5)_3Sn(C_6H_5COO)]$ (**9**), respectively, where in the synthesis of triphenyltin(IV) derivative only one mole equivalent of the benzoic acid was used.

Dibutyltin(IV) dibenzoate (**3**): white solid; UV-Vis λ_{max} . (MeOH) nm (log ϵ): 235 and 274; IR ν_{max} . (KBr) cm^{-1} : 2925.63 (bu), 1628.80 (C=O), 1421.59 (CO_2 asym), 1070.96 (Sn-O-C), 747.88 (Sn-O), 431.19 (Sn-Bu); 1H -NMR (in DMSO- D_6 , 600 MHz) δ (ppm): H_a = 1.60 (t), H_b = 1.54-1.56 (m), H_c = 1.24-1.30 (m), H_d = 0.93 (t), H in benzoate, H_3 and H_7 = 7.90 (d), H_4 and H_6 = 7.7 (t), H_5 = 7.53 (t) ^{13}C -NMR (in DMSO- D_6 , 150 MHz): δ (ppm): C in butyl, C_a = 26.75; C_b = 25.50, C_c = 21.24; C_d = 13.52; C in benzoate C_1 = 164.54; C_2 = 133.00, $C_{3,7}$ = 130.71; $C_{4,6}$ = 128.90, C_5 = 127.93; microelemental analysis, found (calculated): C 48.48 (55.58), H 4.68 (5.89).

Diphenyltin(IV) dibenzoate (**6**): white-light yellow solid; UV-Vis λ_{max} (MeOH) nm (log ϵ): 238 and 279; IR ν_{max} (KBr) cm^{-1} : 1660.80(C=O), 1467.6; 751.3 (phen); 1532.9 (CO₂ asym), 1243.4 (Sn-O-C), 572.6 (Sn-O); ¹H-NMR (in DMSO-D₆, 600 MHz) δ (ppm): H₂ & H₆ 7.59 (d, 4H); H₃ & H₅ 7.48 (t, 4H); H₄: 7.35 (t, 2H), H in benzoate = H₉ and H₁₃ = 7.94 (m), H₁₀ and H₁₂ = 7.84 (t), H₁₁ = 7.65 (t); ¹³C-NMR (in DMSO-D₆, 150 MHz): δ (ppm): C(phen) C₂ & 6: 131.7, C₃ & 5 = 129.3, C₄ = 126.9; C₇: 174.7; C₈: 139.5; C₉ & C₁₃: 130.2; C₁₀ & C₁₂: 129.1; C₁₁: 128.5; microelemental analysis, found (calculated): C 60.41 (60.58), H 3.81 (3.88).

Triphenyltin(IV) benzoate (**9**): white-yellowish solid; UV-Vis λ_{max} (MeOH) nm (log ϵ): 236 and 278; IR ν_{max} (KBr) cm^{-1} : 1631.4 (C=O), 1558.8 (CO₂ asym), 1428.7; 729.6 (phen), 1243.4 (Sn-O-C), 765.6 (Sn-O); ¹H-NMR (in DMSO-D₆, 600 MHz) δ (ppm): H₂ & H₆ 7.59 (d, 4H); H₃ & H₅ 7.48 (t, 4H); H₄: 7.35 (t, 2H), H in benzoate = H₉ and H₁₃ = 7.94 (m), H₁₀ and H₁₂ = 7.84 (t), H₁₁ = 7.65 (t); ¹³C-NMR (in DMSO-D₆, 150 MHz): δ (ppm): C(phen) C₂ & 6: 131.7, C₃ & 5 = 129.3, C₄ = 126.9; C₇: 174.7; C₈: 139.5; C₉ & C₁₃: 130.2; C₁₀ & C₁₂: 129.1; C₁₁: 128.5; microelemental analysis, found (calculated): C 60.41 (63.39), H 3.81 (4.25).

2.3. The antifungal activity test

The procedure of the antifungal activity test undertaken based on the procedure reported previously [10] and as follows: the *F. oxysporum* isolates are available in the botany laboratory, Universitas Lampung. The fungi isolates were taken from their pure culture and transferred to PDA (*Potatoes Dextrose Agar*) media to get their optimum growth. The activity test of organotin(IV) compounds was performed with the disk diffusion test method based on the method we previously performed [10].

3. Results and discussion

The synthesis of organotin(IV) benzoate compounds, **3**, **6** and **9** was successfully carried out following the success of previous synthesis with different ligands [5-10] from starting materials of **1**, **4** and **7** via the intermediate products **2**, **5** and **8**. The reaction that occurred is as shown in Figure 1.

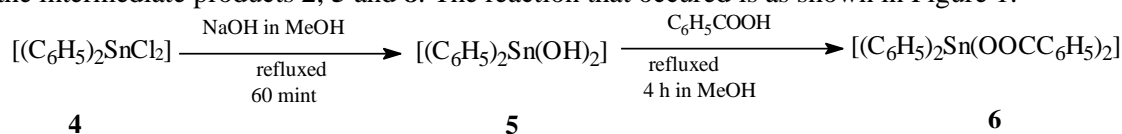


Figure 1. Synthesis route of diphenyltin (IV) dibenzoate compound

The characterization of the products obtained was analyzed using FT-IR spectroscopy in the frequency range 4000 - 400 cm^{-1} . As an example, the characterization of compound **6** as following: the characteristic absorption of the starting material (compound **4**) is the present of the main absorption of the Sn-Cl bond in the region 440-340 cm^{-1} and it was observed that in **4** appeared at a frequency of 346.3 cm^{-1} . When compound **4** is converted into compound **2**, the frequency absorption band 346.3 cm^{-1} is disappeared and a new main absorption appears at 572.6 cm^{-1} which is a typical absorption. from the appearance of the Sn-O bond in compound **5**. While the absorption of phenyl and C = C vibrations are still appeared as expected. After the reaction of **5** and benzoic acid to produce compound **6**, in the IR spectrum, the present very strong vibration band in the region of 1660.8 cm^{-1} is an indication of C=O bond in compound **6**. It is strengthened by the presence of vibration from Sn-O-C bond at 1243.4 cm^{-1} . The similar observations were also observed in the formation of compound **3** and **9**, and these data are agreed to the reported values in the literature [5-10, 16].

The formation of the final product was also confirmed by chemical shifts in the NMR spectra obtained. For example in compound **3**, based on the spectra obtained, the chemical shift (δ) of protons from butyls bound to the Sn atom appeared in the range of 0.93 ppm for H δ up to 1.6 ppm for H α , while the proton in benzoate appeared in the range of 7.7 – 7.9 ppm. These chemical shifts are close to

the data available in the literature. The carbons in the butyl ligands as expected are also observed in the position similar to the chemical shift of similar compounds reported by others [5-10, 17, 18]. The carbon COO- in all compounds are appeared in the chemical shift of about 174 ppm [10, 17-20]. The same observations also apply to compound **6** and **9** which indicated that the success of the synthesis.

The results of antifungal activity test are shown in Table 1, and it is clear that the organotin(IV) benzoate compounds are by far more active than the acid, starting material and intermediate products indicating that the binding of carboxylate to Sn atom plays an important role in the fungitoxicity properties of organotin(IV) compounds.

Table 1. Antifungal activity of the tested compounds

Compound	Activity against <i>F. oxysporum</i>
Benzoic acid	+
(C ₄ H ₉) ₂ SnCl ₂ (1)	+
(C ₄ H ₉) ₂ SnO (2)	+
(C ₄ H ₉) ₂ Sn(C ₆ H ₅ COO) ₂ (3)	+++
(C ₆ H ₅) ₂ Sn(C ₆ H ₅ COO) ₂ (6)	+++
(C ₆ H ₅) ₃ Sn(C ₆ H ₅ COO) (9)	++++

Description: + = low activity, ++ = moderate activity, +++ = high activity, ++++ = very high activity

According to Crowe [21] the actual biological activity of the organotin(IV) with formula RR'SnXY (R and R' = alkyl or aryl; X and Y = anion) is only determined by the RR'Sn²⁺ ion, thus the X and Y groups of the organotin(IV) compound only play a role in the entry of the active group RR'Sn²⁺ or ArAr'Sn²⁺ ions into the cell. The high activity of the organotin(IV) benzoate compound relative to the starting materials (**1**, **4** and **7**), the intermediate compounds (**2**, **5** and **8**) and free benzoic acid seems to be an additional and non-synergistic effect of metal ions [22, 23].

4. Conclusion

The results clearly showed that the organotin(IV) benzoate compounds synthesized had higher antifungal activity than the acid, starting materials and intermediate products. These results further support the results obtained and has been reported in our previous studies. Further research on compounds related to various alkyl and aryl groups as well as various types of carboxylic acids is still and is ongoing in our laboratory.

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