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Synthesis of Novel Organotin (IV) Derivatives of 3, 4- Methylenedioxy-6-Nitrobenzoic Acid and Their Efficacy against Microbes

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The present manuscript deals the synthesis of a novel organotin (IV) derivative of 3.4 methylenedioxy-6-nitrobenzoic acid through modified method followed by their characterization with the help of spectral analysis. The new compounds were also screened for their antimicrobial activity against pathogenic strains of bacteria and fungi at different concentrations to find out their efficacy against Antimicrobial Resistance (AMR). It was found that these compounds show remarkable antimicrobial activity and shows effective against Antimicrobial Resistance with different Structure-Activity Relationship.

Key words: Organotin, pathogenic, antimicrobial resistance, antibacterial, antifungal.

Introduction

Organotin compounds are those compounds containing at least one bond between tin and carbon. The first organotin compound, diethyltindichloride, was synthesized by Frankland in 1849 [1]. The second attempt was made by Lowing in 1852 [2] when he established that ethyl iodide when react with tin/sodium alloy, gave oligomeric diethyl tin oxide and with halogens, gave diethyltindihalides. Organotin compounds, particularly the hydrides, oxides and amides are finding increasing use as reagents in organic synthesis. A number of trialkyltin (IV) compounds are also used industrially in various biological applications, and some dialkyltin(IV) compounds are used for catalyzing certain organic reactions, and as a stabilizers for poly(vinyl chloride).Tin forms predominantly covalent bonds to other elements, but these bonds exhibit a high degree of ionic character with tin usually acting as electropositive. The alkyl groups are usually introduced by complete alkylation of tin tetrachloride with an organometallic reagent, then the various alkyltinchlorides, R_nSnCl_{4-n} (n =1-4), are prepared by the redistribution reaction. Other functional groups are then introduced by nucleophilic of the chloride. Organotin compounds show ionic nature, thus offer dissimilar chemical properties. A useful quick source of references for the synthesis, properties, reactions and application of

about 1000 selected organotin compounds is available in the Dictionary of Organometallic Compounds [3]. The recent developments are reviewed in special periodical reports and journals related to organometallic chemistry [4] covering structural aspects of organotin carboxylates [5-7]. Over the last 30 years, research the chemistry of organometallic compounds of tin in +4 oxidation state has represented one of the most prolific areas of chemical activity. However, the last 10 years have been a steady growth in the number of investigations into the chemistry of organometallic of tri- and diorganotin species.

Experimental

The synthesis of tri and diorganotin (IV) derivatives of 3.4 methylenedioxy-6-nitrobenzoic acid was performed under oxygen free nitrogen atmosphere through modified novel method [8]. There are following reactions representing the synthesis of representative compounds.

Reaction of Triphenyltin(IV)chloride with 3.4 methylenedioxy-6-nitrobenzoic acid:

In the stirring solution of Triphenyltin(IV)chloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light off white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Tris(pentafluorophenyl)tin(IV)chloride with 3.4 methylenedioxy-6-nitrobenzoic acid:

In the stirring solution of tris(pentafluorophenyl)tin(IV)chloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Tris(p-fluorophenyl)tin(IV)chloride with 3.4 methylenedioxy-6-nitrobenzoic acid:

In the stirring solution of tris(p-fluorophenyl)tin(IV)chloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a off-white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Diphenyltin(IV)dichloride with 3.4 methylenedioxy-6-nitrobenzoic acid (1:2):

In the stirring solution of diphenyltin(IV)dichloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (2mmol) was added in the presence of triethylamine (1ml) in toluene and

stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light off white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Diphenyltin(IV)dichloride with 3.4 methylenedioxy-6-nitrobenzoic acid (1:1):

In the stirring solution of diphenyltin(IV)dichloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light off white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Bis(pentafluorophenyl)tin(IV)dichloride with 3.4 methylenedioxy-6-nitrobenzoic acid (1:2):

In the stirring solution of bis(pentafluorophenyl)tin(IV)dichloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Bis(p-fluorophenyl)tin(IV)dichloride with 3.4 methylenedioxy-6-nitrobenzoic acid (1:2):

In the stirring solution of tris(p-fluorophenyl)tin(IV)chloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (2mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 1 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives an off-white solid which was recrystallized by petroleum ether (40-60˚C).

Reaction of Bis(p-fluorophenyl)tin(IV)dichloride with 3.4 methylenedioxy-6-nitrobenzoic acid (1:1):

In the stirring solution of tris(p-fluorophenyl)tin(IV)chloride (1mmol), 3.4 methylenedioxy-6-nitrobenzoic acid (1mmol) was added in the presence of triethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 1 more hr to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives an off-white solid which was recrystallized by petroleum ether (40-60˚C).

Antibacterial Activity:

Antibacterial activity of the synthesized compound was carried out by disc diffusion method [9] using ampicillin as standard. The filter paper (Whatman No.1) sterile disc of 5 mm diameter, impregnated with the test compounds (10 μg/ml of ethanol) along with standard were placed on the nutrient agar plate at 37°C for 24 hrs in BOD incubator. The inhibition zone around the dried impregnated disc was measured after 24 hrs.

Antifungal Activity:

The antifungal activity of the compound was tested by agar plate diffusion method [10], using ampicillin as standard wherein concentration of the test compounds was 50 μg/ml were prepared and tested against two pathogenic fungal strains, Aspergillus flavus and Aspergillus niger. The 1 ml of each compound was poured into a petridish containing 20-25 ml of molten potato dextrose-agar medium. As the medium solidify, petridishes were incubated at 37°C for 96 hrs in BOD incubator. After 96 hrs the colony diameter was measured and % inhibition was calculated using standard method.

Results and Discussion

All the reactions were conducted at room temperature under nitrogen condition and the final products were recrystallized in petroleum ether (40-60°C) or in benzene. The complexes were white and off-white in color, obtained as a solid mass which subsequently crystallized with benzene/pet-ether. The complexes have sharp melting point and were soluble in chloroform and acetonitrile.

Infrared Spectroscopy:

Infrared spectra of the investigated compounds have been recorded from their KBr pellets in range 4000-400cm^{-1}.The coordinating mode of the acids (R'COOH) towards the di-and triorganotin (IV) derivatives can be compared with the infrared spectra of free acids, their metal salts and Organotin compounds. Frequencies assigned to ν_{asym}(COO) and ν_{sym}(COO) have been identified in free ligand acids and the synthesized compounds. They are reported together with bands assigned to ν(Sn-C) and ν(Sn-O) in table. The explicit feature observed in the spectra of all the compounds in absence of the broadband in range 2504-3034 cm^{-1}, which appears in free ligand acid as ν(O-H)-position thus indicating metal ligand bond formation through this site. Moreover, absorption bands which appear in the synthesized compounds in the range 498-427 cm^{-1} and 597-501 cm^{-1}, assigned to Sn-O and Sn-C bonds, respectively, which support the formation of complexes.

UV Spectra:

The electronic spectra obtained for representative compound was recorded in chloroform in the range 200-400nm. The UV absorption due to COO group appears at 274+6 and 294+2. On the basis of IR, NMR and UV spectral analysis data, it may be concluded that the present study behaves as a monodentate ligand.

^{1}HNMR Spectroscopy:

^{1}HNMR spectra for synthesized compounds have been recorded in $CDCl_3$ and DMSO solution. ^{1}HNMR response signals of the protons attached to the phenyl moieties of the ligands have been assigned by their distinct multiplicities, J -values and comparisons with the results obtained from the incremental method.

^{13}C NMR Spectroscopy:

^{13}C NMR Spectra recorded in $CDCl_3$ and DMSO solutions of the free ligands and their respective di- and triorganotin (IV) derivatives. The ^{13}C NMR Spectral data for the R group attached to the tin atom where R = Ph, (C_6F_5) and (f-C_6H_4) were assigned by comparison with related analogues as model compounds, combined with the ″J [^{119}Sn, ^{13}C] coupling constants. The positions of the phenyl, pentafluorophenyl and p-fluorophenyl carbon signals undergo minor variations in the complexes as compared to those observed in the free acids and their sodium salts. The carboxylate carbon shifts to lower fields almost in all the complexes indicates the participation of the carboxyl group (COO) in the coordination to tin (IV).

^{119}Sn NMR Spectroscopy:

The possibility of detecting the presence of coordinative different organotin (IV) moieties was explored by acquisition of ^{119}Sn NMR spectra for all the investigated compounds. The ^{119}Sn NMR spectra were recorded in $CDCl_3$ solution, a non-coordinating solvent. The ^{119}Sn chemical shift values obtained for the triorganotin (IV) derivatives lie in the range expected for a tetrahedral geometry where as diorganotin (IV) compounds show higher coordination. The geometric data calculated are consistent with tetrahedral geometries for the triorganotin (IV) species and for the diorganotin(IV) species, for which earlier results indicated five-coordination consistent with the skew-trapezoidal bipyramidal geometries, a lower coordination number become apparent arising from the asymmetric coordination mode of the carboxylate ligands.

Antibacterial activity:

The compounds show higher to moderate activity against the bacterial strains. It was found that compound with water and lipid solubility is more effective. It generally form complexes with metaloenzymes, particularly those which responsible in basic physiology such as cytochrome oxidase. The compound may react with peptidoglycan layer of bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it followed by death of bacterial cell. Sometimes these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.

Antifungal Activity:

The activity of compound was found variable at 50μg/ml concentration but at higher concentration compound show moderate to high activity against fungal strains. Presence free chloride, phenyl ring along with metal in variable oxidation state are considered for fungal activity. The role of ligand was also commendable. These compounds generally damage the fungal strains by puncturing the cell wall similarly as in the case of bacteria.

Conclusion

The newly synthesized tri- and diorganotin(IV) carboxylates were novel and show prominent antimicrobial activity against pathogenic bacterial and fungal strains showing potential efficacy against antimicrobial resistance.

Table-1: Physicochemical Properties of new organotin (IV) carboxylates

S.N.	Compounds	Formula Weight	Yield (%)	M.P. (^{0}C)	Elemental Analysis		
					C%	H%	N%
1	$C_{26}H_{19}O_6NSn$	560	72	110	55.71	3.39	2.50
2	$C_{26}H_4O_6NF_{15}Sn$	830	70	97	37.59	0.48	1.68
3	$C_{26}H_{16}O_6NF_3Sn$	614	75	106	50.81	2.60	2.28
4	$C_{28}H_{18}O_{12}N_2Sn$	693	70	102	48.48	2.59	4.00
5	$C_{20}H_{14}O_6NSnCl$	518.5	72	118	46.28	2.70	2.70
6	$C_{28}H_8O_{12}N_2F_{10}Sn$	873	75	94	38.48	0.91	3.20
7	$C_{20}H_4O_6NF_{10}SnCl$	698.5	65	98	34.35	0.57	2.00
8	$C_{28}H_{16}F_2O_{12}N_2Sn$	729	68	96	46.09	2.19	3.84
9	$C_{20}H_{12}F_2O_6$ NSnCl	554.5	70	114	43.28	2.16	2.52

Table-2: Infrared Data (cm-1) a of Organotin(IV) Carboxylates

S.N.	Compounds	ν(COO)		Δν	νSn-C	νSn-O
		asym	sym			
1	$C_{26}H_{19}O_6NSn$	1620s	1412m	190	577m	445m
2	$C_{26}H_4O_6NF_{15}Sn$	1624m	1424m	200	550w	450m
3	$C_{26}H_{16}O_6NF_3Sn$	1610s	1414s	196	545w	485m
4	C28H18O12N2Sn	1620s	1423m	197	527m	453w
5	$C_{20}H_{14}O_6NSnCl$	1590s	1403s	187	552w	442w
6	C28H8O12N2F10 Sn	1620m	1425s	195	560m	468m
7	$C_{20}H_4O_6NF_{10}SnCl$	1609s	1420s	189	563w	445w
8	C28H16F2O12N2 Sn	1619m	1427m	192	564w	480w
9	$C_{20}H_{12}F_2O_6$ NSnCl	1592m	1406s	186	545w	443m

Table-3: Antibacterial activity of organotin (IV) carboxylates

S.N.	Compound	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Klebsiela pneumoniae*
1	$C_{26}H_{19}O_6NSn$	11.00±0.57	8.10±0.16	12.00±1.15
2	$C_{26}H_4O_6NF_{15}Sn$	11.33±0.66	11.00±0.57	08.50±0.29
3	$C_{26}H_{16}O_6NF_3Sn$	08.00±0.28	19.00±0.57	13.00±0.50

4	C28H18O12N2Sn	17.33±0.6	19.00±0.57	15.00±0.57
5	$C_{20}H_{14}O_6NSnCl$	18.66±0.66	07.83±0.44	10.5±0.76
6	C28H8O12N2F10Sn	15.66±0.33	16.00±0.57	17.00±0.57
7	$C_{20}H_4O_6NF_{10}SnCl$	11.00±0.57	08.10±0.16	12.00±1.15
8	C28H16F2O12N2Sn	10.94±0.48	08.04±0.10	11.88±0.70
9	$C_{20}H_{12}F_2O_6$ NSnCl	11.33±0.66	11.00±0.57	8.58±0.29
10	Untreated Control	No inhibition	No inhibition	No inhibition
11	Ampicillin (standard)	18.0±0.21	12.66±0.50	16.26±0.30

Table-4: Antifungal Activity of organotin (IV) carboxylates 50µg/ml concentration

S.N.	Compounds	Aspergillus flavus Col. Dia. (mm)	% Inhibition	Aspergillus niger Col. Dia.(mm)	% Inhibition
1	$C_{26}H_{19}O_6NSn$	0.2	93.3	0.4	80.0
2	$C_{26}H_4O_6NF_{15}Sn$	0.1	96.7	0.2	90.0
3	$C_{26}H_{16}O_6NF_3Sn$	0.1	96.7	0.1	95.0
4	$C_{28}H_{18}O_{12}N_2Sn$	0.5	83.3	0.4	80.0
5	$C_{20}H_{14}O_6NSnCl$	0.4	86.7	0.1	95.0
6	$C_{28}H_8O_{12}N_2F_{10}Sn$	0.6	80.0	0.5	75.0
7	$C_{20}H_4O_6NF_{10}SnCl$	0.4	86.7	0.2	90.0
8	$C_{28}H_{16}F_2O_{12}N_2Sn$	0.5	83.3	0.4	80.0
9	$C_{20}H_{12}F_2O_6$ NSnCl	0.1	96.7	0.4	80.0
10	Control (Ampicillin)	3.0	--	2.0	--

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