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ORGANIC CHEMISTRY | RESEARCH ARTICLE

Studies of the mechanism of the reduction of different thioxanthen-9-ones

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Abstract: 2-Propoxythioxanthen-9-one (**1**), 2-chloro-4-methylthioxanthen-9-one (**2**) and tributylstannyloxythioxanthene (**3**) were reduced to 2-propoxythioxanthen (**1′**), 2-chloro-4-methylthioxanthen (**2′**) and thioxanthen (**3′**) using dibutyltin chloro hydride. The mechanism of this reaction involving formation of tributylstannyloxy-thioxanthyl ketyl radical has been suggested by comparison of products of hydro-stannation of three studied thioxanthene derivatives.

Subjects: Chemistry; Organic Chemistry; Physical Sciences

Keywords: thioxanthen-9-ones; thioxanthene; dibutyltin chloride hydride; reduction

1. Introduction

Lucanthone (Miracil D) (Berberian, Freele, Rosi, Dennis, & Archer, 1967; Haidle, Brinkley, & Mandel, 1970; Hirschberg et al., 1968) and hycanthone (Etrenol) (Archer, Pica-Mattoccia, Cioli, Seyed-Mozaffari, & Zayed, 1988; Hirschberg & Weinstein, 1971; Rosi et al., 1967; Ruas, 1972; Turner, Bases, Pearlman, Nobler, & Kabakow, 1975), which are derivatives of thioxanthenone are known as antischistosomal and anticancer agents. With the discovery of curative anticancer activities in animal modes, this series of compounds, like WIN 33377, were advanced into clinical trials (Izbicka, Lawrence, Davidson, Rake, & Von Hoff, 1998; Perni et al., 1998; Stevenson et al., 1999; Wentland et al., 1994).

The exact mechanism of action of these compounds is unknown; however, some members of this family of compounds preferentially inhibit DNA synthesis and mammalian topoisomerase type II. Presumably, thioxanthen-9-ones during such processes undergo reduction into thioxanthenes.

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ABOUT THE AUTHORS

We study the catalytic influence of solvation effects and the addition of inorganic salts on: ene reactions of olefins (photo-oxidation and amination); ene reactions of aldehydes and ketones (allylstannylation); metalloene reactions of allyltin compounds; metalloene reactions of tin phenoxides (amination and vinylation); hydrostannylation of ketones and alkynes using tin hydrides; free radical additions leading to formation of new carbon–carbon bonds carried out with Bu_3SnH as a coreagent.
Additionally, we study the catalytic effect of properties of liquid binary mixtures of organic solvents on photo-oxidation of olefins. These works are linked with studies on physicochemical properties of liquid binary mixtures.

Dr. Wojciech J. Kinart, who is a supervisor of our research group, is the author of 120 papers and three books cited about one thousand times.

PUBLIC INTEREST STATEMENT

Organotin hydrides, due to their high stability, prove to be invaluable reagents in different chemical reactions, such as reduction of functional groups and many others which extend free radical mechanism. Dialkyltin dihydrides R_2SnH_2, readily react with suitable compounds R_2SnX_2 where X is an electronegative group, such as halide, carboxylate or sulfonate. This leads to a large variety of hydrides R_2SnXH, which are more reactive than simple tributyltin hydride. Thioxanthenones such as these contained in a plant as biologically active Miracil D and Etrenol are compounds widely known because of their anticancer properties and use in the treatment of schistosomiasis. The use of thioxanthenones as sensitizers in manufacturing of paint shows another possibility of application of these compounds. The objective of the present work was to determine the mechanism of reduction of studied thioxanthene-9-ones using dibutyl chloride hydride.

The use of thioxanthenones as sensitizers in production of inks shows another possible application of these compounds. For example, 1-chloro-4-propoxythioxanthen-9-one (Green & Timms, 1993; Green, Timms, & Green, 1991) exhibits higher activity when compared to 4-isopropylthioxanthenone, which is generally regarded as the industrial standard for these systems. In fact, thioxanthen-9-one photosensitizer initiates polymerization of vinyl monomers during such processes.

Yates and Schuster (1984) reported that thioxanthenone triplet is photoreduced by amines via chargetransfer or exciplex intermediate to thioxanthyl ketyl radical. Formed thus, thioxanthenol or ditioxanthyl pinacol are easily oxidized materials. The former is reported to disproportionate on heating to thioxanthene and thioxanthenone. Oehlschlaeger and MacGregor (1950) reported a simple method of reduction of thioxanthenone to 10-thioxanthenol by sodium. Recently, Marcinek, Rogowski, Adamus, Gębicki, and Platz (1996) demonstrated spectroscopically, the intermediacy of the transition radical cation in sequential oxidation processes upon photolysis of thioxanthene. Similar stepwise oxidation processes have also been demonstrated for other NADH analogues (Fakuzami, Tanaka, Fox, & Chanon, 1998). A quantitative oxidation of thioxanthene during such process leads to thioxanthenone. Previously, we have carried out the comparative studies on the hydrostannation of different thioxanthenones by Bu_2SnClH (Kinart, Kinart, Kozak, & Kinart, 2009). However, no clear mechanism of this reduction was presented. In recent years, the organotin hydrides found extensive applications in organic synthesis which involve radical chain reactions in which the stannyl radical is a chain-carrying intermediate. The hydrides R_2SnXH (X = e.g. chloride) can be formed by the comproportionation between diorganotin dihydrides, R_2SnH_2, and the compounds R_2SnX_2 (Scheme 1).

These reactions usually occur readily at room temperature as natural processes in human body involving conversions of anticancer agents.

2. Experimental

2.1. Caution

Although we did not encounter any problem with $LiAlH_4$, hydrides are potentially hazardous and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood.

Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 600 MHz spectrometer using tetramethylsilane (TMS) as an internal standard.

2.2. General procedure for synthesis and reductions

2-Propoxythioxanthen-9-one (**1**), 2-chloro-4-methylthioxanthen-9-one (**2**) were commercial samples. Tributylstannyloxythioxanthene (**3**) was prepared by reduction of commercial thioxanthen-9-one with $LiAlH_4$ and azeotropic dehydration carried out in benzene of a mixture of obtained thioxanthen-9-ol with $(Bu_3Sn)_2O$.

Dibutyltin dihydride was prepared by treatment of dibutyltin dichloride with lithium aluminium hydride in over 50% excess as described by van der Kerk, Noltes, and Luijten (1957). Subsequent ether extraction and distillation gave required dihydride in quantitative yield.

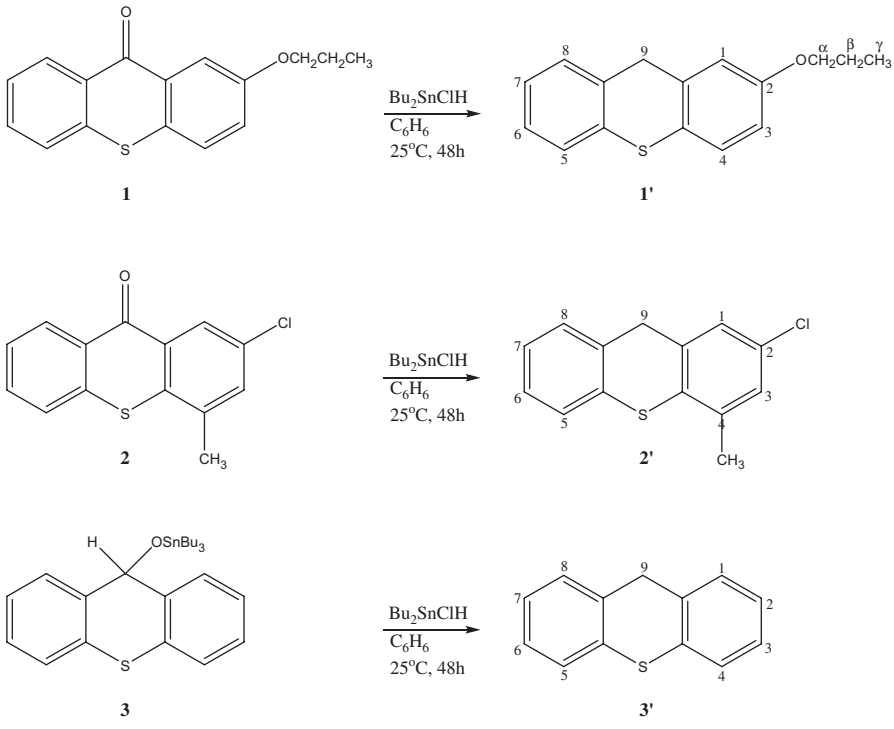
Scheme 1. The hydrides R_2SnXH obtained by the disproportion reaction between diorganotin dihydrides, R_2SnH_2, and the compounds R_2SnX_2.

Dibutyltin chloride hydride was prepared by disproportion reaction between dihydride and dibutyltin dichloride (Sawyer & Brown, 1966). The equilibrium was reached within few minutes and it was shifted towards Bu_2SnClH (Scheme 2).

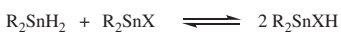
We have carried out reduction 2-propoxythioxanthen-9-one (**1**), 2-chloro-4-methylthioxanthen-9-one (**2**) and tributylstannyloxythioxanthene (**3**) using dibutyltin chloro hydride (Bu_2SnClH).

A typical example of reduction of studied compounds is as follows: 235 mg (1 mmol) of dibutyltin dihydride (Bu_2SnH_2) and 303 mg (1 mmol) dibutyltin dichloride were added to 10 ml of benzene. After 30 min, when the equilibrium leading to formation of Bu_2SnClH was reached, 270 mg (1 mmol) of 2-propoxythioxanthen-9-one (**1**) was added. The progress of the reaction was monitored by TLC and ^{1}H-NMR spectroscopy. After 48 h, the product of the reaction was purified by column chromatography using a mixture of ethyl acetate and petroleum ether (3/7, v/v). The product obtained in quantitative yield was identified as 2-propoxythioxanthene (**1′**). The same procedure was repeated for 2-chloro-4-methylthioxanthen-9-one (**2**) and tributylstannyloxythioxanthene (**3**). It led to formation of 2-chloro-4-methylthioxanthene (**2′**) and thioxanthene (**3′**), respectively. The products were characterized on the basis of their elemental analysis and ^{1}H-NMR spectral analysis (Scheme 3).

Scheme 2. Dibutyltin chloride hydride obtained by the disproportion reaction between dihydride and dibutyltin dichloride.



Scheme 3. Reduction of different thioxanthenones using dibutyltin chloride hydride.



2.3. Spectroscopic data of products are given below

2-Propoxythioxanthene (1′) ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 1.41–1.48 (2H, m, β-CH_2), 1.14 (3H, t, *J* = 6HZ, γ-CH_3), 4.03 (2H, t, *J* = 6Hz, α-CH_2), 4.09 (2H, s, 9-H), 7.18–7.23 (1H, m, 7-H), 7.23–7.27 (2H, m, 3-H, 6-H), 7.37 (2H, dd, *J* = 7.4, 1.9 Hz, 4-H, 5-H), 7.48 (2H, dd, *J* = 7.4, 1.9 Hz, 1-H, 8-H).

2-Chloro-4-methylthioxanthene (2′) ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 2.32 (3H, s, –CH_3), 3.80 (2H, s, 9-H), 7.03–7.07 (4H, m, 1-H, 3-H, 7-H, 8-H), 7.30 (1H, td, *J* = 7.5, 1.5, 6-H), 7.62 (1H, dd, *J* = 7.5, 1.5, 5-H).

Thioxanthene (3′) ^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 3.86 (2H, s, 9-H), 7.12–7.20 (2H, m, 2-H, 7-H), 7.20–7.22 (2H, m, 3-H, 6-H), 7.32 (2H, dd, *J* = 7.4, 1.9 Hz, 4-H, 5-H), 7.44 (2H, dd, *J* = 7.4, 1.9 Hz, 1-H, 8-H).

Low-resolution mass spectra (MS) of (**1′**), (**2′**) and (**3′**) were taken using chemical ionization (Cl) technique with Finningan MAT 95 instrument (source temperature of ca. 200°C, reagent gas-isobutan, accelerating voltage of 4.8 kV). MS (Cl) m/z = 255.3, 245.1, 197.1 (M-1) corresponding to above-mentioned thioxanthenes. Calculated values of (M-1) were equal, respectively, to 255.5, 245.7 and 197.3.

4. Results and discussion

The products of reduction of two chosen thioxanthen-9-ones (**1**), (**2**) and tributylstannyloxythioxanthene (**3**) by tributyltin chloride hydride (Bu_2SnClH) have been identified as thioxanthenes (**1′**), (**2′**) and (**3′**).

We have previously (Kinart et al., 2009) observed the analogous course of the reduction for thioxanthen-9-one, 2-chlorothiohanthen-9-one and 1-chlorothioxanthen-9-one by Bu_2SnClH.

We were presently anxious to suggest a definite mechanism of reduction of studied thioxanthen -9-one.

In the purpose to choose or exclude the mechanism involving formation of ketyl radical during such reduction, we have reduced thioxanthen-9-one to thioxanthen-9-ol using $LiAlH_4$. Further azeotropic dehydration in benzene of a mixture of thioxanthen-9-ol with bis(tributyltin) oxide gave 9-tributylstannyloxythioxanthen. Its reduction with Bu_2SnClH led directly to thioxanthene. It seems to indicate the formation of the ketyl radical as an intermediate product, similarly as it has been reported by Yates and Schuster (1984) during photoreduction of thioxanthenones.

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