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Molecular Design for a Novel Organotin Hydride

Introduction

The history of organotin hydride began in the year 1922 with the synthesis of trimethyltin hydride, Me₃SnH, by Kraus and Greer. Since then organotin hydride has evolved multidimensionally, and has achieved recognition worldwide as a credible reagent in synthetic organic chemistry.

There are several ways of preparation of organotin hydrides, but the most convenient one is reducing the corresponding tin halide by employing a complex metal hydride such as LiAlH₄, NaBH₄, R₂AlH or B₂H₆.

Organotin hydrides are versatile reagents. They can react at the hydrogen centre with electrophiles, nucleophiles, or free radicals. All the processes are important in organic synthesis, but the recent chemistry of the hydrides has been dominated by the radical reactions which provide important procedures in synthetic organic chemistry. Some well appreciated reaction of organotin hydrides are addition reaction to multiple bonds, reactions with protic acids and bases, hydrostannolysis of organic halides, etc.

Simple trialkyltin hydrides are marred by separation, toxicity and disposal problems. These problems prompted chemists to look for ways out and the continuing saga of search for newer pastures included modifications in the workup procedures, using catalytic amount of tin hydride or its precursor with stoichiometric amount of another hydride, using fluorous tin hydrides, water soluble tin hydrides, and polymer supported
tin hydrides. In the past nine decades of the history, organotin hydrides have evolved from simple versions such as trialkyltin hydrides to versions which are much more complex but do have fascinating properties.

Asymmetric synthesis is a key component of today’s chemistry. To make organotin hydrides compatible in such synthesis, chiral organotin hydrides are being designed and developed to achieve enhanced enantioselectivity. Chiral organotin hydrides can serve as enantioselective reducing agents under free radical environment. Reagents which are chiral solely at the tin tend to undergo ready racemisation, and so most of the chiral tin halides and hydrides, which have been evaluated to date for asymmetric synthesis, have made use of chiral ligands on the tin.

The idea of creating an organotin hydride with structure I.1 was conceived based on the fact that the molecule without tin-nitrogen coordination lacks steric rigidity and hence directional property in its reactivity. It is expected that in a molecule like I.1, in which Sn and N lie within bonding distance, N would coordinate to tin and this would facilitate a more efficient and stereoselective hydrogen transfer during the reduction process.

The proposed synthesis of target tin hydride I.1 necessitated the development of a methodology that could be used to synthesize molecule I.3 in large quantities and high purity. Three different approaches were attempted.
(i) One step synthesis of conjugate addition of triphenyltin hydride to alkyl propiolate under free radical condition initiated by AIBN.

(ii) Coupling of alkyl glyoxylates with (dibromomethyl)triphenylstannane under the reaction conditions developed by Hodgson and co-workers. This approach essentially involves a three-step process requiring the syntheses of alkyl glyoxylate and (dibromomethyl)triphenylstannane prior to the coupling reaction.

(iii) A multistep process starting with the preparation of \((E)-3\)-triphenylstannylprop-2-en-1-ol which can be oxidized to \((E)-3\)-triphenylstannylprop-2-en-1-al and then to \((E)-3\)-triphenylstannylprop-2-enoic acid. Esterification of this acid will then lead to target ester 1.3.

Strategies (i) and (iii) were successful, and (iii) was found to be better as compared to strategy (i).

Results and Discussion

\((E)-3\)-Triphenylstannylpropenoic acid 1.21 was synthesized in an overall yield of 45% in three steps. Hydrostannation of propargyl alcohol by triphenyltin hydride under free radical condition initiated by AIBN afforded \((E)-3\)-triphenylstannylprop-2-en-1-ol 1.19 in 58% yield. The alcohol 1.19 was oxidized to aldehyde \((E)-3\)-triphenylstannylpropenal 1.20 by manganese dioxide in 89% yield and the aldehyde 1.20 to acid 1.21 by sodium chlorite in 88% yield. The acid 1.21 could be coupled with \((R)-pantolactone by DCC to form \((R)-pantolactonyl ester 1.27 in 85% yield and reacted with trimethylsilyldiazomethane to form methyl \((E)-3\)-triphenylstannylpropenoate 1.3 in 91%
yield. The acid was also coupled with benzylamine and diethylamine mediated by DCC to corresponding amides in 62% and 18% yields respectively. However, coupling with pyrrolidine was not successful.

\[ \text{Ph}_3\text{Sn} \equiv \text{OH} \quad \text{Ph}_3\text{Sn} \equiv \text{CHO} \]

\[ \text{Ph}_3\text{Sn} \equiv \text{CO}_2\text{H} \quad \text{Ph}_3\text{Sn} \equiv \text{CHO} \]

Diels-Alder reaction of aldehyde I.20 with cyclopentadiene gave 3-triphenylstannylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde I.50 in 92% yield with 85% selectivity in favour of the endo-aldehyde. Similarly Diels-Alder reaction of ester I.3 with cyclopentadiene gave methyl 3-triphenylstannylbicyclo[2.2.1]hept-5-ene-2-carboxylate I.34 in 95% yield with 88% selectivity in favour of the endo-ester. The endo-ester I.34 was alkylated exclusively from the endo-face to afford methyl 2-benzyl-3-triphenylstannylbicyclo[2.2.1]hept-5-ene-2-carboxylate I.36 in 74% yield by enolization with lithium diethylamide followed by alkylation with benzyl bromide. The structure of ester I.36 was established by single crystal X-ray diffraction.
The ester I.36 was converted to aldehyde 2-benzyl-3-triphenylstannylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde I.42 by reduction with DIBAL to corresponding alcohol followed by Swern oxidation in 89% yield over two steps. The aldehyde I.42 was reacted with hydrazine hydrate to form a hydrazone but did not react with N,N-dimethylhydrazine to form N,N-dimethylhydrazone. It could be made to react with hydroxylamine hydrochloride and methoxyamine hydrochloride with great difficulty to form oximes (1RS,2RS,3RS,4SR)-3-benzyl-2-chlorodiphenylstannylbicyclo[2.2.1]hept-5-ene-3-carbaldehyde oxime I.45 and (1RS,2RS,3RS,4SR)-3-benzyl-2-chlorodiphenylstannylbicyclo[2.2.1]hept-5-ene-3-carbaldehyde O-methyloxime I.47 respectively. The oxime formation with hydroxylamine hydrochloride was accompanied by replacement of one of the phenyl groups in triphenylstannyl moiety by chlorine. Formation of O-methyloxime by treating with methoxyamine hydrochloride was also accompanied by replacement of a phenyl group by chlorine to some extent. The structures of these oximes have been studied by single crystal X-ray diffraction. X-ray diffraction studies of oximes have revealed that strong intramolecular interaction does exist between the Sn-atom and the N-atom of the oxime functionality.

Unsuccessful attempts were made to convert the ester I.36 to an amide, to an acid and also to a seleno-ester. Similarly reductive amination to afford an amine and oxidation
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to form an acid on aldehyde 1.42 were unsuccessful. Efforts made to convert aldehyde 1.50 to an enamine and to reduce oximes, and hydrazones derived from aldehyde 1.42 were without any success.

Conclusion
The flexibility and the range of applicability possessed by organotin hydrides have no match. In this investigation, an attempt was made to add yet another feature to the flexibility and applicability of organotin hydrides.

Ordinarily organotin hydrides lack configurational rigidity, and hence directional property in hydrogen transfer, which is so essential in stereoselective reduction processes. An intramolecular coordination between the tin atom and a suitably positioned heteroatom may be an effective measure to instill configurational rigidity in organotin hydrides, and this should help to determine the trajectory of hydrogen transfer from the tin hydride so as to facilitate a more efficient and stereoselective reduction process.

This investigation has established that the tin atom in an organotin compound has a natural bending to coordinate with a suitably positioned N-atom within the molecule. En route to achieve the designer tin hydride, two organotin compounds, compound 1.45 and compound 1.47, were synthesized. In both the compounds, crystallographic study shows significant bonding interaction between the tin and the nitrogen atom. Further investigation will be necessary to convert these compounds to tin hydrides, or more works to synthesize tin hydrides with similar design, but the road-map is printed here for the future investigators.
Ferric Chloride Mediated Michael Addition of Dicarboxylic Acid Esters
to α,β-Unsaturated Ketones

Introduction

The Michael addition reaction, one of the most studied and widely applied C-C bond forming reactions was introduced into synthetic organic chemistry more than a century ago by Michael himself in 1880s, and first report appeared in the year 1887. When introduced, the reaction was defined by Arthur Michael as the addition of an enolate of a ketone or a aldehyde to the β-carbon of an α,β-unsaturated carbonyl compound. Since then in the past more than a hundred years old history, the scope of the Michael addition reaction has been widened to cover a large number of substrates and reagents. The Michael addition is now defined as the addition of a nucleophile, including non-carbon nucleophiles, to the β-position of a carbon-carbon double bond of an α,β-unsaturated ketone, aldehyde, nitrile, or carboxylic acid derivatives. It belongs to the larger class of conjugate additions.

The Michael addition reactions are catalyzed by both Lewis acids and Lewis bases, and several procedures involving such catalysts are reported in literature. Most of the reported nucleophiles are carbon-nucleophiles, which are carbanions, and often derived from compounds containing active methylene groups or organometallics. Some favourite pro-nucleophiles are malonates, β-keto esters, cyano esters, nitroalkanes, thiols, etc. Silyl enolates have also been reported as nucleophiles. Other versions of Michael addition reaction such as aza-Michael addition, oxy-Michael addition involve N-
nucleophile and O-nucleophile respectively in place of usual C-nucleophiles. These versions of Michael additions are also considered as a powerful tool for the carbon-heteroatom bond forming reactions.

Results and Discussion

Ferric chloride catalyzed Michael addition of allenates with Grignard reagents is reported but ferric chloride catalyzed Michael addition of \(\alpha,\beta\)-unsaturated ketones with malonates and succinates could not be traced. In this part of the thesis ferric chloride hexahydrate catalyzed Michael addition of dimethyl malonate (DMM) and dimethyl succinate (DMS) to a couple of \(\alpha,\beta\)-unsaturated ketones, both in dichloromethane and methanol, have been examined and discussed. The general representation of the reaction is shown in Scheme II.1.

\[
\begin{align*}
R = & \text{Me, Ph} \\
X = & \text{H, OMe, Cl, NO}_2, \text{Me, OH} \\
\text{II.1} & \\
\text{II.2 } n=0 & \\
\text{II.3 } n=1 & \\
\text{II.4 } n=0 & \\
\text{II.5 } n=1 & \\
\text{A: DCM, rt} & \\
\text{B: Methanol, reflux} & 
\end{align*}
\]

Scheme II.1

\(\alpha,\beta\)-Unsaturated ketones, nineteen in total, used in this investigation were prepared in the laboratory. Dimethyl malonate (DMM) II.2 and dimethyl succinate (DMS) II.3 were also prepared in the laboratory.
Michael addition of dimethyl malonate to sixteen different α,β-unsaturated ketones to form dimethyl 2-(3-oxo-1-phenylbutyl)malonates (II.4a to II.4p) were carried out successfully in both dichloromethane (DCM) and methanol in the presence of 20% of ferric chloride hexahydrate as the mediator. While the reactions in DCM proceeded smoothly at ambient temperature to afford moderate to high yield (72 - 88% in 30 to 50 h), the yields of same reactions in methanol at ambient temperature were inherently low (less than 70%) and reaction time was also considerably high (more than 50 h). Yields in methanol could however be considerably increased at reflux temperature (62 - 84%) with simultaneous decrease in reaction time as well (30 - 45 h). Other solvents such as acetonitrile and toluene were also tried but yields were always low. 20 mol% catalyst was considered optimal. More than 20 mol% catalyst concentration did not help.

Michael addition of dimethyl succinate were examined with twelve different α,β-unsaturated ketones to form dimethyl 2-(3-oxo-1-phenylbutyl)succinate (II.5a to II.5k) both at room temperature in dichloromethane (DCM), and at refluxing temperature in methanol. All the reactions, except the one with chalcone proceeded smoothly, posed no complexity in workup and afforded excellent yields (77 to 92%). It is worth mentioning that, unlike malonate, succinate does not undergo Michael addition with chalcone and chalcone derivatives.

Results achieved at refluxing temperature of methanol were moderate to high yields (67 to 88%), and were achieved in 40 to 50 h of refluxing time. If compared with results at room temperature in DCM, it appears that the reactions should better be carried out in DCM at room temperature albeit longer reaction time. However, environmental
aspect associated with DCM may be a deterrent factor, and one would better opt for methanol at refluxing temperature needing to sacrifice of about 5 to 10% yield.

**Conclusion**

Defined as the Lewis acid- or Lewis base-catalyzed nucleophilic addition to the β-carbon of an α,β-unsaturated carbonyl compound, Michael addition reaction has exceeded every chemist’s expectation in its flexibility and applicability in synthetic organic chemistry. Countless catalysts and innumerable nucleophiles are now in record for use in Michael addition reactions according to one’s requirement and convenience. However, it is highly intriguing to notice that succinic acid esters are missing from the long list of nucleophiles used in Michael additions. It is equally intriguing to find that ferric chloride, a non-hazardous chemical and widely used Lewis acid, has never been reported as a catalyst in any Michael addition of malonates, a widely appreciated pro-nucleophile in a large number of Michael addition reactions.

During this investigation, ferric chloride has been examined as a catalyst in sixteen different Michael addition reactions involving malonic acid methyl ester as the pro-nucleophile, and eleven different reactions involving succinic acid methyl ester as the pro-nucleophile. Thus, this investigation has established ferric chloride as an effective Lewis acid catalyst in Michael addition reactions of malonic acid and succinic acid methyl esters.

Michael addition of succinic acid ester-derived nucleophile to an α,β-unsaturated carbonyl compound generates two chiral centers in a single step reaction to afford a functionally dense molecule. Such a Michael adduct can be a much sought-after building
block in the synthesis of complex and large natural and bioactive molecules. This investigation has established succinic acid methyl ester as a credible pro-nucleophile in several Michael addition reactions. Further work to examine stereoselectivity in these reactions would only add more colour to this investigation, which is an initiation only to show the tip of an ice berg.