Organic Reactions in Aqueous Medium
&
Development of New Ditribromide Reagent

Submitted by

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Abstract

The contents of this thesis have been divided into two chapters summarizing the results based on the experimental works performed during the complete course of the research period. Each chapter constitutes four sections, sections **A-D** describing introduction, present work, experimental work and spectral data respectively. Organic transformations in aqueous medium are the theme of first chapter in which various synthetically useful reactions such as tetahydropyranylation of alcohols and syntheses of tertiary amines are described. The second chapter describes the synthesis of newer tribromide reagent and its utilization in various organic transformations such as bromination, synthesis of benzothiazole from thiourea and thioamide, diacylation of aldehydes and synthesis of various xanthene derivatives from enalizable ketones and 9-phenyl xanthene-9-ol.

CHAPTER I

Part (I): Organic Reactions in Aqueous Medium

Section IA: Introduction

Water plays an essential role in life processes; however its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest and most non toxic solvent in the world, its presence is generally avoided through dehydration of substrates and solvents. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists. For years limited organic transformations has been performed in water as a reaction medium. Breslow has demonstrated that the hydrophobic effect accelerates the rate of Diels-Alder reaction and gives high endo-exo selectivity. Despite the solubility problems of organic substrates in water after the seminal contribution of Breslow, new additions are continuously being made to the catalogue of organic reactions that can be performed effectively with water as the solvent.

Tetrahydropyranyl ethers (THP ethers) were one of the first generally useful protecting groups for alcohols to be adopted. The easy installation as well as facile and selective removal of these ethers renders them attractive in complex organic synthesis. In addition tetrahydropyran derivatives are less expensive, and stable under a variety of reaction conditions such as strongly basic media, metal hydrides, Grignard reagents, acylating agents, oxidative and alkylating agents. The only drawback is the formation of an additional stereocentre that may lead to diastereomeric mixtures if

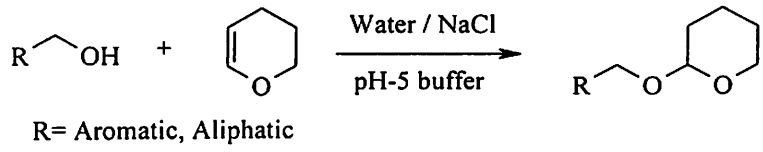
the alcohol already possesses a stereogenic centre. This complicates the NMR spectra and hence makes its interpretation difficult. In spite of this detraction, it is the most extensively and frequently used protecting group for alcohols.

Amines are one of the most common structural features of naturally occurring biologically active compounds and are widely used throughout the chemical industry as a basic intermediate to prepare pharmaceutically and agro chemically useful chemicals. Due to their unique biological properties, amines have played an important role as chemotherapeutic agents for the treatment of various diseases. They are useful agents for potentiation of opiate analgesia, treatment of extrapyramidal movement disorders, besides, of course their use as antifungal, general anesthetic, antipsychotic, antihistamic and calcium channel blocking agents. Indeed no less than a quarter of the registered drugs contain tertiary amine. Thus, the development of new synthetic routes to these pharmaceutically important compounds has stimulated constant interest and has been the focus of many research groups over the years.

Section 1B: Present Work

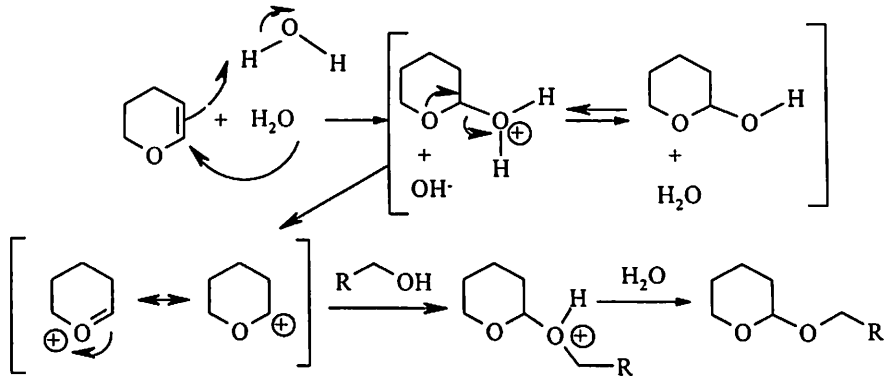
1B.1. Water as Catalyst and Solvent: Tetrahydropyranylation of Alcohols in an Aqueous Medium

This part of the thesis describes the utilization of water as catalyst and solvent for tetrahydro pyranylation of alcohols. Tetrahydropyranylation is usually performed in anhydrous aprotic organic solvents because of the longer reaction time and poor yields of product obtained in the presence of water. Based on the pKa's of water (15.74), alcohols (~16.5), protonated hydroxyls of 2-hydroxy tetrahydropyran (~ -2) and protonated ethereal functions (~ -6), we speculate that pyranylation of alcohol should occur in an aqueous medium and due to an unfavorable pKa phenol should not undergo tetrahydro pyranylation in water (Scheme 1B. 1 and 2). Water is found to catalyze the tetrahydropyranylation of alcohols at elevated temperature. Interestingly, tetrahydropyranylation of alcohols works under a wide range of pH examined *i.e* 6.5 to 2 and do not work beyond pH 7.5 in aqueous medium. Hydrophobic interactions between the substrate alcohol and dihydropyran ether (DHP) and favorable pKa's of water, alcohols, and protonated hydroxyl and protonated ethereal functions are the driving forces for the reaction.



R= Aromatic, Aliphatic

Sheme1B.1. *Formation of THP ether in water*



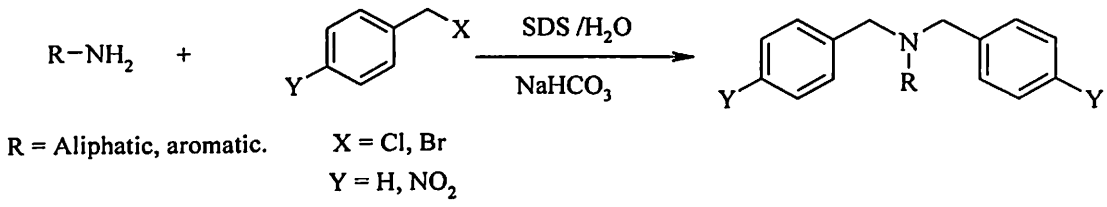
Scheme 1B.2. *Mechanism of formation of THP ether in water*

This method has advantage of using highly acidic pH to weakly acidic pH and can even be carried out in pure water without using any acidic or basic reagents hence most acceptable from environmental point of view for the development of green strategies. Thus the reaction, which is carried out in anhydrous aprotic solvents, can be carried out in aqueous medium in an environmentally benign way. Besides understanding the reaction mechanism, mild reaction conditions, simplicity of the procedure, general applicability for a wide range of alcohols and selective mono-tetrahydropyranylation of diols offer significant advantages over many existing procedures.

1B.1.2. Aqueous Mediated N-Alkylation of Amines

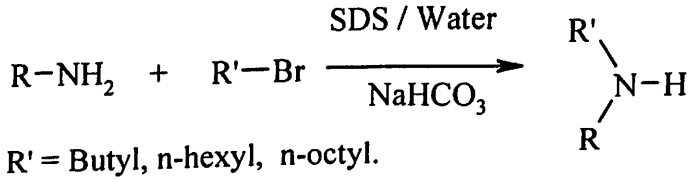
This section of thesis focused on N-alkylation of amine in an aqueous medium. The efficient dissolution of amines in an aqueous medium and its subsequent acylation using various anhydrides by our group prompted us to perform N-alkylation in an aqueous medium. Initially, alkylation was

performed using benzyl bromide. Various conditions were sampled, but a 1: 2.2: 2.2 ratio of substrate to benzyl halide to $NaHCO_3$ at 80 °C gave best result. Using this optimized reaction conditions we were able to alkylate structurally diverse primary and secondary amines with different benzyl halides to their corresponding tertiary amines (Scheme 1B.3). Amines of different stereo-electronic factors react with equal ease with different benzyl halides. The synthetic step includes a two steps alkylation of primary amine with benzyl halide through intermediate secondary amine.



Scheme 1B.3. *N-Alkylation of primary amines to tertiary amines with benzyl halides*

Having successfully applied to benzylic systems, we extended this methodology to aliphatic halides. Under the reaction conditions to that of benzylic system, the products obtained were a mixture of tertiary and secondary amines in the ratio 3 : 2. The products ratio remained nearly unaltered even after refluxing the reaction for 12 hours. Thus, we focused our attention to controlling it at the secondary amine rather than at the tertiary amine stage. Thus, a 1 : 1 : 1.3 ratio of substrate to alkyl bromide to $NaHCO_3$ using above conditions gave exclusively secondary amines in good yields. It may be noted here that reaction of alkyl bromides took relatively longer reaction time as compared to benzyl halides.



Scheme 1B.4. *N-Alkylation of primary amines to secondary amines with alkyl halides*

The general nature of the reaction is shown by the intramolecular double-alkylation of primary amines with dihalides such as 1,5-dibromopentane and 1,6-dibromohexane giving corresponding cyclic amines. Allyl bromide also reacted successfully with various amines giving good yields of diallylated tertiary amines. As suggested earlier and proved by isolating some of the

secondary amines, the synthetic steps include a two steps alkylation of primary amine with alkyl halide through an intermediate secondary amine. To further prove this we reacted some of the secondary amines with benzyl and allyl bromide to obtain good yields of mixed tertiary amines containing three different substituents.

In conclusion, we have demonstrated an efficient and economic process for the synthesis of secondary and tertiary amines by direct N-alkylation of primary amines or secondary amines with various benzyl halides, alkyl halides and dihalides in an aqueous medium in the presence of sodium dodecyl sulfate and $NaHCO_3$. Mild reaction conditions, higher product yields, scalability, absence of quarternary ammonium salt and operationally convenient conditions are some of the advantages. Selective formation of secondary amines and mixed tertiary amines will find useful applications in organic synthesis.

CHAPTER II

Development of New Ditribromide Reagent

Section IIA: Introduction

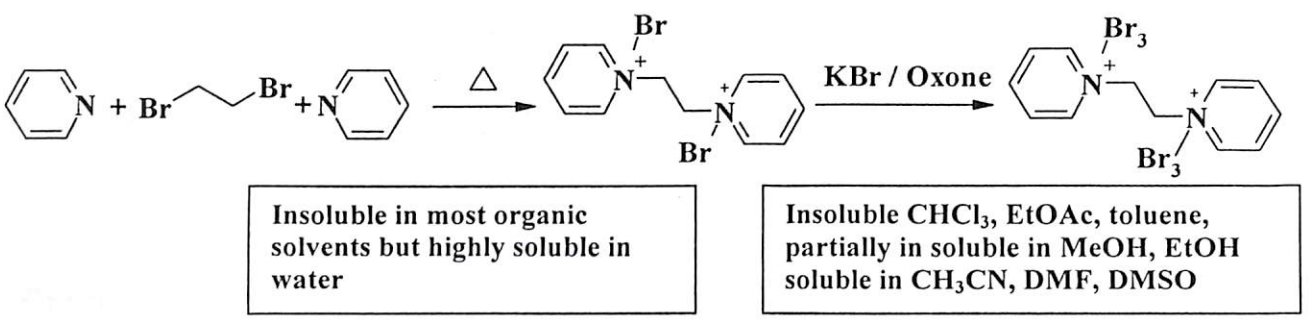
Organic ammonium tribromides are the attractive solid bromine less brominating agents. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of the desired stoichiometry and the ease in storage, transportation and handling. Apart from bromination, tribromides also can be used for several organic transformations such as oxidation of sulfides and alcohols, brominative cyclizations, intramolecular cyclizations. These reagents are an efficient generator of anhydrous HBr in alcohols and many other organic solvents whose acidity can be tuned to a wide range of pH that can be utilizes for various acid catalyzed organic transformations.

Problems associated with the existing organic ammonium tribromides are the use of expensive organic ammonium cations and the use of one third of it's total bromide for an aromatic electrophilic substitution type reaction and two third of it's bromide towards addition to C–C multiple bonds. Some of the organic ammonium tribromides have phase transfer property hence a substantial amount gets extracted along with the organic products in an organic solvent during workup, there by making the purification process tedious and the method expensive for large scale reaction. Recovery

and recycling of expensive organic ammonium cation is also poor after the reaction. Pyridinium tribromide is not so stable compared to other organic ammonium tribromide and reported to have three different melting points and different bromine composition. To over come the phase transfer property, poor stability, regio and stereoselectivity, recovery, and recycling of the spent reagent we have synthesized a novel di-tribromide reagent.

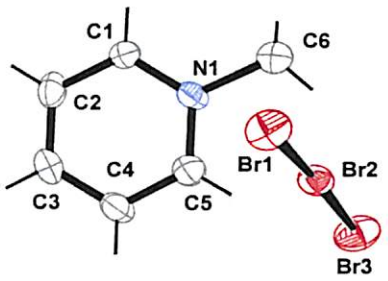
Section IIB: Present Work

IIB.1. A New Recyclable Ditribromide Reagent for Efficient Bromination Under Solvent Free Condition



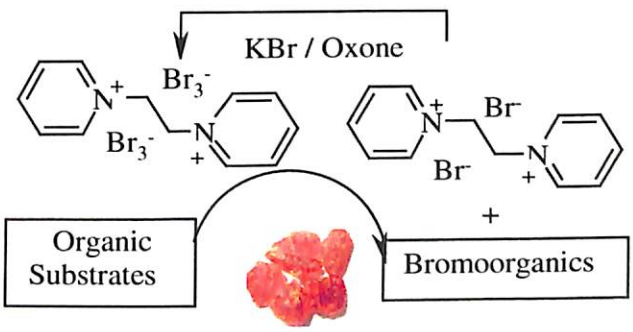
Scheme 11B.1. *Synthesis of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)*

This section focuses on the synthesis of the reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) and its utilization for the bromination of various organic compounds. The reagent can be prepared by refluxing pyridine (2 equiv.) with 1,2-dibromoethane (1 equiv.). The resultant solid 1,1'-(ethane-1,2-diyl)dipyridinium bisbromide (EDPBB) and KBr (4.5 equiv) was dissolved in water and treated with Oxone® (2 equiv) which oxidizes bromide to bromine. The *in situ* liberated bromine gets trapped forming precipitate of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (Scheme 11B.1). The orange precipitate was filtered and was recrystallized from acetonitrile. The compound has been characterized by spectral and analytical data. Single crystal X-RD revealed the presence of two linear tribromide per molecule. Scheme 11B.2.



Scheme 11B.2. *ORTEP diagram of asymmetric unit of EDPBT with atom numbering*

The crystalline ditribromide reagent is stable for months and acts as a safe source of bromine requiring just 0.5 equiv for bromination per equivalent of substrate. It has high active bromine content per molecule and shows a remarkable reactivity compared to other tribromide reagents towards various substrates (phenols, anilines, alkenes, alkynes, ketones) by just grinding the reagent and substrates in a porcelain mortar at room temperature. No organic solvent has been used during any stage of the reaction for substrates giving product as solid. Product can easily be isolated by just washing the highly water soluble 1,1′-(ethane-1,2-diyl)dipyridinium bisbromide (EDPBB) from the brominated product. The spent reagent can be recovered, regenerated and reused without any significant loss (Scheme 11B.3).



Scheme IIB.3. *Bromination of organic substrates using EDPBT*

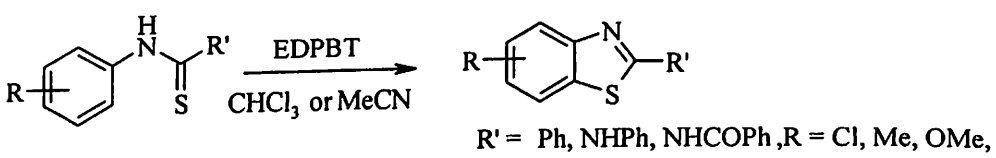
In summary, we have for the first time reported a ditribromide reagent with high active bromine content per molecule, which acts as an excellent bromine carrier capable of brominating an equivalent of the substrate with just half an equivalent of the reagent. The reaction is carried out under a solvent free condition. Selectivities and reactivities were shown to be far superior to any of the reported reagents and methodologies. It has unique features of providing enhanced yields, reduction in synthesis temperatures, shorter process times and environmentally friendly process. The

spent reagent EDPBT can be easily recycled, hence the process is economically viable for large-scale reaction.

IIB.2. Synthesis of 2-Substituted Benzothiazoles Using the Recyclable Reagent EDPBT

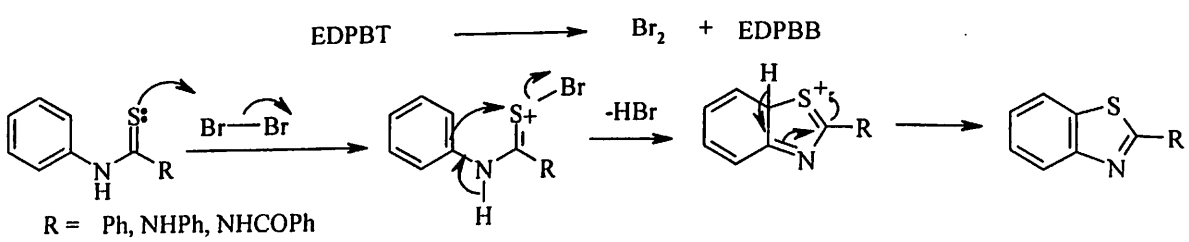
In this part EDPBT has been utilized for the conversion of thioamides and thioureas to benzothiazole derivatives. Benthioazoles are found in various natural products and are important in the drug discovery research. They are precursors to natural products, pharmaceutical agents and other compounds that exhibit a wide spectrum of biological activity.

Due to its numerous applications, several procedures have been developed for their synthesis. The important ones are: (i) by the condensation of 2-amino thiophenol with aromatic carbonyl moiety; (ii) oxidative cyclization of thioureas and thioamides and (iii) intramolecular aryl thiolation. Although many synthetic strategies are available for synthesis of benzothiazoles, the oxidative cyclization of thiomides and thioureas are preferred. The first reported synthesis of benzothiazole is by Hugerschoff method using molecular bromine and arylthiourea. We have used bromine less oxidative cyclization strategy. Various 2-sustituted benzothiazoles were obtained in good yields by reacting thioamides and thioureas with 0.5 equivalent of EDPBT either in $CHCl_3$ or in acetonitrile at elevated temperature (Scheme II B.4).



Scheme IIB.4. *Formation benzothiazole*

The proposed mechanism is shown in Scheme II B.5.

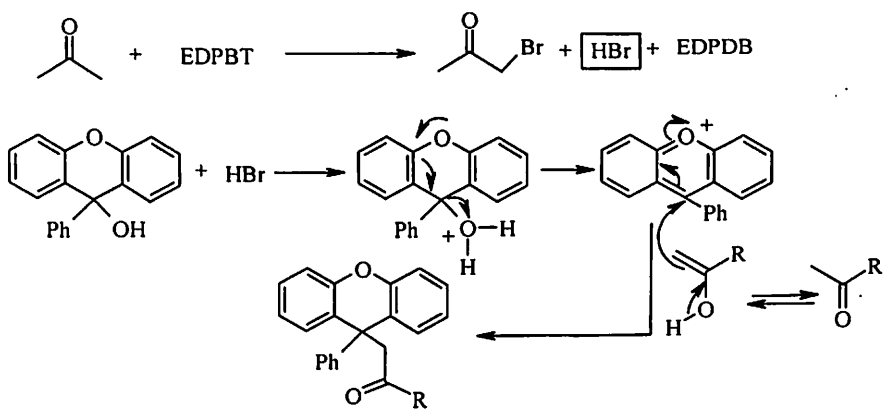


Scheme IIB.5. *Mechanism of formation of benzothiazoles*

Products are obtained in good yields and spent reagent can be recovered and regenerated for further reaction. Problem of handling toxic bromine, metal catalysts both toxic and expensive can be avoided by this method.

IIB.3. Syntheses and Regiochemistry of Enol Addition to Xanthene

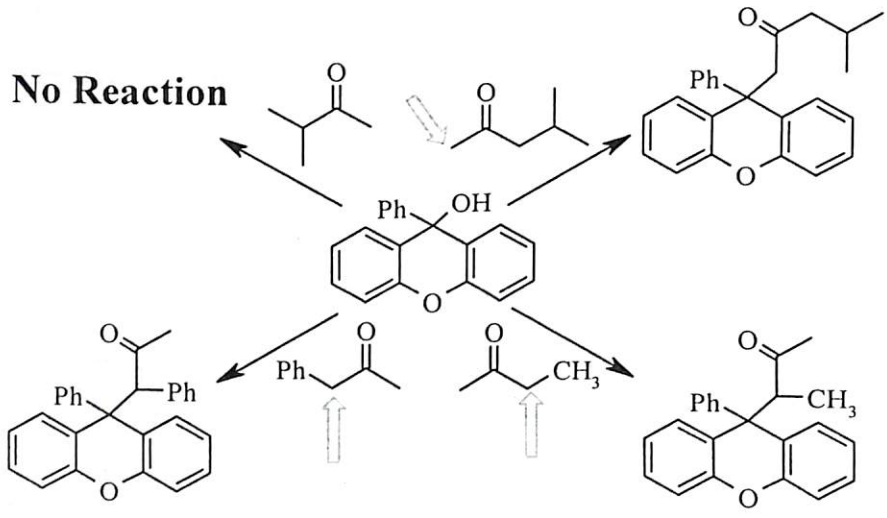
In this part of the dissertation we have focused our attention on the syntheses and regiochemistry of various enol addition to 9-phenyl-9H-xanthen-9-ol and analyzed the self assembled super structures of the addition products in solid state. Xanthene derivatives are useful pharmaceuticals such as, muscarinic receptor antagonist, cancer chemotherapy, trypanothione reductase inhibitor, and chemosensitizers against chloroquine-resistant Plasmodium falciparum, nonpeptidic inhibitors, as mGluR1 enhancer and CCR1 antagonist. They are also useful as dyes, photosensitizers, as ligand for asymmetric catalysis and have the propensity to form inclusion compounds with various aromatic compounds.



Scheme IIB.6. *Plausible mechanism of enol additon to 9-phenyl-9H-xanthen-9-ol*

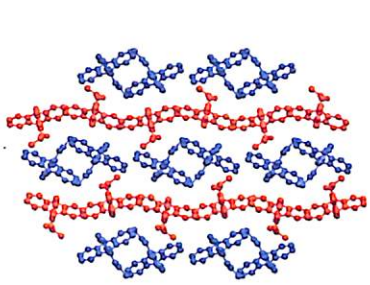
In an attempt to acetylate 9-phenyl-9H-xanthen-9-ol employing acetic anhydride in acetone and 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) as catalyst gave no trace of acetylated product, rather an unusual three carbon homologation was observed. The proposed mechanism of product formation is shown in (Scheme IIB.6).

Being buoyant by this result we focused our attention to synthesize various xanthene analogues. Various multi carbon homologation of 9-phenyl-9H-xanthen-9-ol were obtained through a C-C bond formation by reacting it with various enolizable ketones (acetone, 2-butanone, isobutylmethyl ketone, acetophenone, cyclopentanone, cyclohexanone, phenyl acetone and dibenzyl ketone) in presence of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). Except for isobutylmethyl ketone in all other cases examined the attack to xanthenyl carbocation is from the thermodynamically stable enolizable side of unsymmetrical ketones. Due to complete shift in equilibrium in favor of more stable enolizable ketone which has large steric factor, no reaction was observed during the addition of isopropylmethyl ketone with 9-phenyl-9H-xanthen-9-ol (Scheme IIB.7).

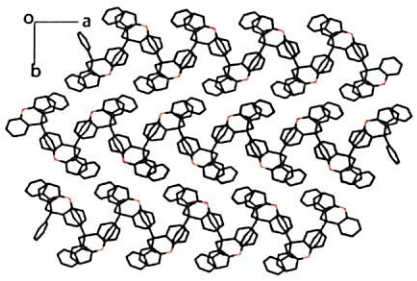


Scheme IIB.7. *Summary of the regiochemistry of enol addition to xanthen*

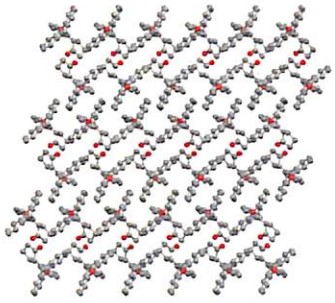
All the addition products obtained were highly crystalline compounds. During the course of structural analysis of 9-phenyl-9H-xanthen-9-ol and its derivatives they were found to be synthons for supramolecular design. In order to delineate our objectives of supramolecular synthons, we have carried single crystal X-ray diffraction studies of all the products along with its starting compound. Critical investigation of the solid state structure can help us to reveal the effect of variation of alkyl and aryl appendage on the supramolecular assembly / crystal engineering. The supramolecular assemblies of the addition products held by weak non covalent interactions are shown below (Figure IIB.1).



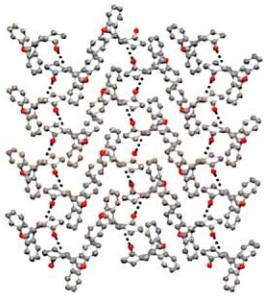
Crystal packing in acetone adduct



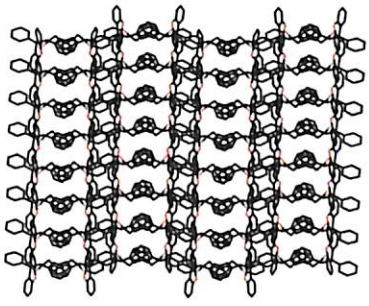
Crystal packing in acetophenone adduct.



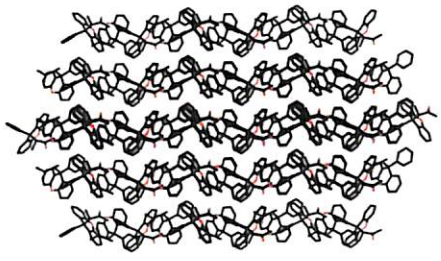
Crystal packing in cyclopentanone adduct.



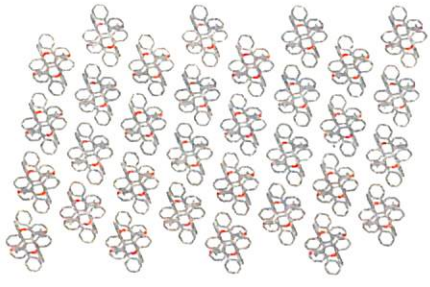
Crystal packing in cyclohexanone adduct



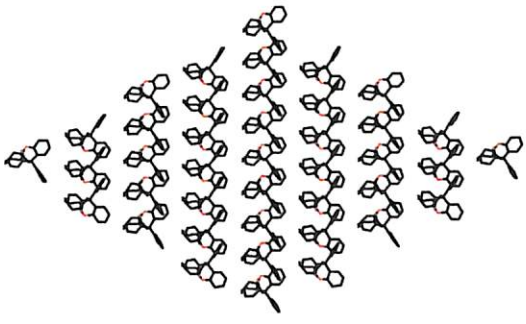
Crystal packing in dibenzyl acetone adduct



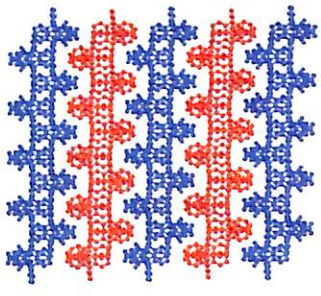
Crystal packing in butanone adduct



Crystal packing in phenyl acetone adduct



Crystal packing in isobutyl methyl ketone adduct



Crystal packing in ethyl aceto acetate adduct

Figure IIB.1. *Crystal packing in different xanthene derivatives*

In conclusion, we have achieved multicarbon homologation of 9-phenyl-9H-xanthen-9-ol through a C–C bond formation by various enolizable ketones in an acidic medium. Regiochemistry of the product can be explained with the help of kinetic and thermodynamic stability of the enol. X-ray crystallography of all the products revealed the disposition of the pendant group in the opposite

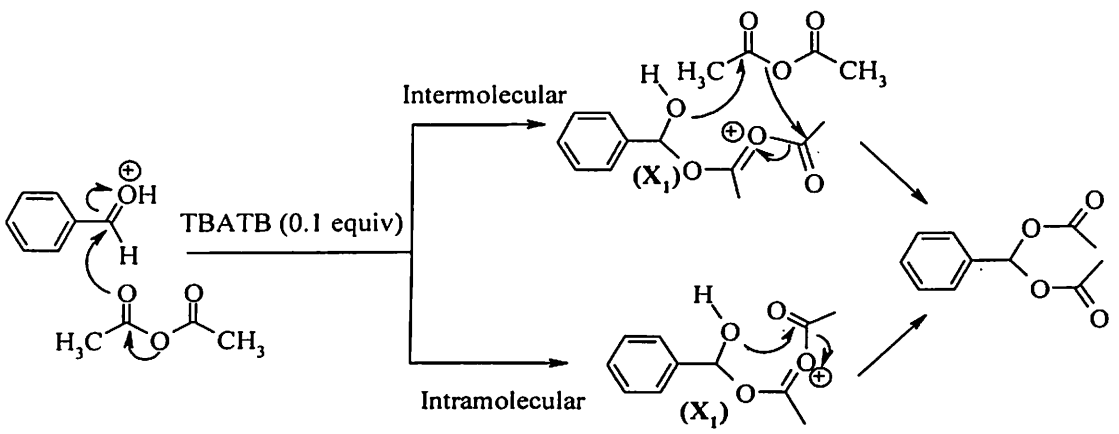
direction with respect to the xanthene unit to relive the steric crowding in the solid state. The precursor xanthene and its derivatives serve as an interesting supramolecular synthons and contain remarkable systems of interconnectivity by conventional and non-conventional hydrogen bonds. A programmed variation in the side arm of the xanthene derivatives results not only in interesting regiochemistry of addition products but also lead to self-assembled superstructure by different types of weak interactions.

IIB.4. Reinvestigation of the Mechanism of *gem*-Diacylation: Chemoselective Conversion of Aldehydes to Various *gem*-Diacylates and Their Cleavage under Acidic and Basic Conditions

The mechanism of the formation of *gem*-diacylate, the addition product of acid anhydride with aldehyde is not yet well understood. *Gem*-diacylate functionalities have served as an interesting protecting group for aldehydes in addition to acetals, oxathioacetals and thioacetals. Unlike acetal protecting group which is removed only under acidic conditions, *gem*-diacylates can be removed both under acidic and basic conditions. The *gem*- diacylate of aldehydes are useful precursors for nucleophilic substitution reactions, used in the synthesis of acetoxydienes, vinyl acetates and dienes for Diels-Alder reaction and also used as several industrial intermediates. Due to the remarkable stability of *gem*-diacetates towards a variety of reaction conditions and their easy preparation, they are gaining importance in organic synthesis as an alternative to cyclic and acyclic acetals for protection of aldehydes. It is superior over acetals because during acetalization, the water formed in the reaction medium is required to be removed either by physical or by chemical means using water scavengers such as orthoformates, that is not required during *gem*-diacylation of aldehydes.

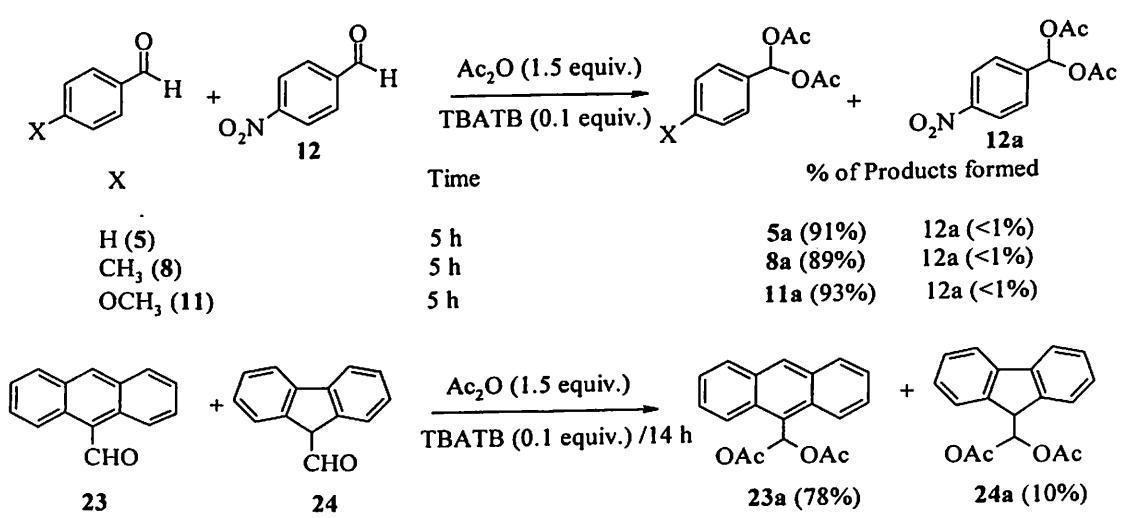
In the past he mechanism of *gem*-diacylation has been a subject of some controversy. In this part, we have reinvestigated the mechanism of *gem*-diacylate formation using tetrabutylammonium tribromide (TBATB), which liberates acid in the reaction medium to catalyze the reaction. Two plausible mechanisms could be thought of for *gem*-diacylation, one involving an intramolecular and other an intermolecular transfer of a second acylate group after the initial nucleophilic attack by an anhydride on an aldehydic group as proposed in Scheme IIB.8. After a series of experiments an intermolecular mechanism has been postulated. The reaction proceeds by a nucleophilic attack of an anhydride on an aldehydic carbonyl group, nucleophilic attack of the hemiacylate intermediate on a

second molecule of an anhydride, followed by an intermolecular attack of a second acetate group to regenerate the anhydride.



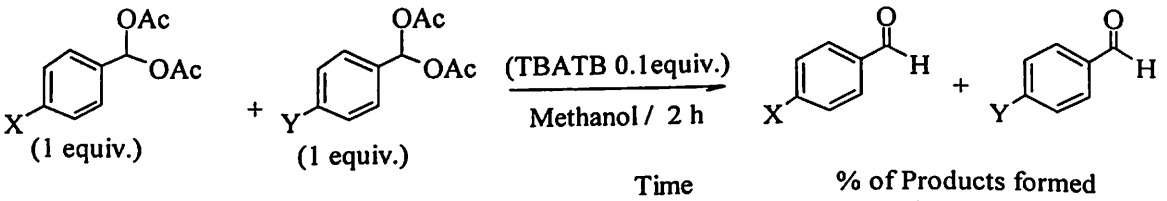
Scheme IIB.8. *Mechanism of formation for the Diacylation*

Gem-diacylates of various aliphatic and aromatic aldehydes were obtained directly by reacting with a variety of aliphatic and aromatic acid anhydrides in the presence of a catalytic quantity of tetrabutylammonium tribromide (TBATB) under solvent free conditions. Significant electronic effect was observed during its formation as well as deprotection to the corresponding aldehyde. Chemoselective *gem*-diacylation of the aromatic aldehyde containing an electron-donating group has been achieved in the presence of an aldehyde containing an electron-withdrawing group which could be seen in Scheme IIB.9.



Scheme IIB.9. *Chemoselective gem-diacylation of aldehydes*

Deprotection of *gem*-diacylate to the parent carbonyl compound can be accomplished in methanol in the presence of the same catalyst. Here again, chemoselective deprotection of *gem*-diacylate of the substrate containing an electron-donating group has been achieved in presence of the substrate containing an electron-withdrawing group as shown in Scheme IIB.10.



	Time	% of Products formed
X=CH_3 (**8a**) + Y=NO_2 (**12a**)	2 h	**8** (90%) + **12** (00 %)
X=OCH_3 (**11a**) + Y=NO_2 (**12a**)	2 h	**11** (90%) + **12** (00 %)

Scheme IIB.10. *Chemoselective deprotection of gem-diacylates*

Both the acid and base stability order of various *gem*-diacylates examined follows the similar order. The stability order determined from the present study is: *gem*-dibenzoate > *gem*-dipivalate > *gem*-diisobutyrate > *gem*-diacetate > *gem*-dipropionate. All the *gem*-diacylals are more stable under basic condition than acidic condition. No correlation was found between the stability order and the pKa's of the corresponding acids; rather, the stability order is directly related to their steric crowding around carbonyl carbon.

In conclusion we have demonstrated the mechanism of gem diacylation of aldehydes and the *gem*-diacylates of various aliphatic and aromatic aldehydes can be prepared from a variety of aliphatic and aromatic anhydrides under solvent free conditions in the presence of a catalytic quantity of tetrabutylammonium tribromide (TBATB). Deprotection of *gem*-diacylates to the corresponding parent carbonyl compounds has been accomplished by performing the reaction in methanol with the same catalyst. We also demonstrated the stability of diacylates derived from the cinnamaldehyde. Diacylates are more stable under basic conditions than acidic conditions. Interestingly, both acid and base stability of various gem-diacylates follow the same order, The stability order obtained from a series of competitive experiments is: *gem*-dibenzoate > *gem*-dipivalate > *gem*-diisobutyrate > *gem*-diacetate > *gem*-dipropionate, and is directly related to the steric crowding around the carbonyl carbon rather than to the pKa of corresponding acid.