3. An environmentally friendly synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones using iodine – A simple and readily available catalyst

3.1. Effect of Solvent on the Rate of Chemical Reactions

3.1.1. Introduction

While planning an organic reaction, one of the major concerns to chemists is the choice of solvent and this is not without a reason. Well, the role of solvents in the organic reactions is really crucial, which is beyond the boundaries of words. However, first of all, let’s consider the basic properties and functioning of the solvents. Basically, a solvent is a liquid, gas or solid which dissolves another liquid, gas or solid solute resulting in a solution. Majority of the solvent reactions are performed in solutions. Solvents play essential roles in chemical processes not only serving to put reactants into contact by dissolution but also affecting rates, chemo-, regio- and stereoselectivities of the reactions. Solvents are also used in the later stages of a reaction, which means in the extraction and purification of the products.\(^1\)

Apart from water, there are some organic solvents, which can affect the rate of chemical reactions. Usually, these solvents have a low boiling point and they evaporate easily. As soon as the solvent reactions are completed, they can be removed by the process of distillation, which leaves the dissolved substance behind, solvents are generally present in the greater quantity.

As a reaction medium, a solvent may be used in a number of ways. For example, in endothermic reactions, heat could be supplied through a heated inert solvent having a high heat capacity, while in exothermic reactions, the surplus heat can be removed by allowing the solvent to boil or absorb heat. If reactions involve solid reactants, solvents could be used to create a reaction medium through which the solid reactants can be brought into contact. Similarly, gas phase reactions, which are normally at high temperatures and/or pressures, could be performed in the liquid phase under significantly lower temperatures and/or pressures. Also, reactants that are too reactive in one solvent could be safely studied in another solvent. Finally, solvents may be used to indirectly influence the reaction by removing one or more products on-site.\(^2\)

Following the Green Chemistry Principles when organic solvents must be employed, their use must be minimised and optimised to enhance the reactions with the minimum environmental and operational concerns. The important factors to be taken into account when choosing a solvent for organic synthesis are as follows:
3.1.1.1. Solvent selection

Given the details of an organic reacting system such as nature of reactants, products, reaction kinetics, etc.), the objective is to find solvents that can promote the reaction in terms of yield, reaction mass efficiency.\(^2\)

3.1.1.2. Reaction-solvent properties

Properties of solvents have an important role in the selection and evaluation that may be added to a reaction system. The reaction-solvent properties considered are described below.\(^2\)

3.1.1.3. Reactivity of the solvent

For those situations where the solvent has an indirect influence on the reaction, the selected solvent must be neutral to the reactants, products and inerts present in the reacting system.\(^2\)

3.1.1.4. Solvent must be liquid at the reaction conditions

Boiling point, melting point and vapour pressure of the solvent and the reaction system will verify whether the solvent will be in the liquid phase at the reaction conditions.\(^2\)

3.1.1.5. Solubility of reactants or product

The solvent selected should mostly dissolve the reactants and not the product thereby facilitating the isolation of the products with ease devoid of starting materials. But in the case of a non-isolation reaction that is to be followed by additional reactions that may be carried out in the same reaction vessel the solvent should be capable of dissolving the intermediate product as well. In other situations, it may be better to make the product completely or mostly insoluble in the solvent system. For example, adding a solvent/anti-solvent mixture where the solvent dissolves the reactants and the anti-solvent promotes the precipitation of the product as is the case for the production of Ibuprofen.\(^2,3\)

3.1.1.6. Heating/cooling properties of the solvent

Solvents may be used in the reaction as carriers of heat. For example, to supply heat to an endothermic reaction or to absorb heat of an exothermic reaction.\(^2\)
3.1.1.7. Association/dissociation properties of the solvent

Another property of the solvent to check under reactivity is that, the solvent should not associate/dissociate (for example, ionic compounds), polymerise (compounds with double/triple bonds) and/or oligomerise (for example, isomers) under the conditions of the reaction system.\(^2\)

Apart from the environmental concerns, solvents still continue to play an important role in organic synthesis.

3.2. Recent reports on organic reactions carried out in organic solvents

Below are mentioned a few reactions in organic synthesis which are carried out in organic solvents and published recently in the most highly regarded organic chemistry journals

3.2.1. Cross metathesis

A diverse set of functionalized \(\alpha,\beta\)-unsaturated carbonyl compounds were synthesized in good yield by utilizing a very simple one-pot process involving a cross-metathesis between acryloyl chloride and a terminal olefin followed by the addition of a nucleophile in CH\(_2\)Cl\(_2\) (Scheme 3.1).\(^4\)

\[
\text{Acryloyl chloride} + \text{Terminal olefin} \xrightarrow{\text{5 mol\%}} \text{Functionalized carbonyl compound} \xrightarrow{1.6-6 \text{ eq. NuH}} \text{Amine}
\]

Scheme 3.1

3.2.2. Hydrogen transfer reaction

Thiourea-catalyzed transfer hydrogenation of imines through hydrogen-bonding activation with Hantzsch 1,4-dihydropyridine as the hydrogen source has been reported by Z. Zhang and P. R. Schreiner (Scheme 3.2). A variety of aromatic as well as aliphatic aldimines have been reduced to respective amines by an acid- and metal-free reaction conditions.\(^5\)
3.2.3. Protection

Thioacetalization and Transthioacetalization

H. Firouzabadi et al have reported the I\(_2\) catalyzed transformation of aromatic and aliphatic aldehydes and ketones, \(O, O\)-acetals, \(O, O\)-ketalas, \(O, S\)-acetals, and acylals to their thioacetals at room temperature (Scheme 3.3). The reactions could be performed in different organic solvents such as CHCl\(_3\), CH\(_2\)Cl\(_2\), benzene, and n-hexane.\(^6\)

\[
\begin{align*}
\text{Y} & \quad \text{Y} \\
\text{R} & \quad \text{R'} \\
\text{n} : & \quad 1, 2 \\
\text{Y} & \quad \text{OMe, OEt, OAc} \\
\text{YY} : & \quad \text{O, O(CH}_2\text{)}_3\text{O, O(CH}_2\text{)}_3\text{S}
\end{align*}
\]

Scheme 3.3

3.2.4. Deprotection of dioxanes

An efficient method for the cleavage of \(p\)-methoxybenzylidene (PMP), tetrahydropyranyl (THP) and 1,3-dithiane protecting groups by Selectfluor\textsuperscript{TM} (1-Chloromethyl-4-fluoro-1,4-diazeniabicyclo[2.2.2]octane bis(tetrafluoroborate)) in acetonitrile has been developed by J. Liu and C.-H. Wong (Scheme 3.4).\(^7\)

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{PMP} & \quad \text{2.4 eq. Selectfluor} \\
\text{CH}_3\text{CN / H}_2\text{O (95 : 5)} & \quad \text{r.t., 5 h}
\end{align*}
\]

Scheme 3.4
3.2.4.1. Deprotection of Dithianes

Fraser F. Fleming et al. have reported an efficient bis(trifluoroacetoxy)iodobenzene-mediated hydrolysis of a variety of dithiane-containing alkaloids in CH$_3$CN ([Scheme 3.5]).

\[
\text{Scheme 3.5}
\]

3.2.5. Coupling reactions

Substoichiometric amounts of ZnCl$_2$ is used by A. D. Finke et al. to promote the room temperature, Pd/P(t-Bu)$_3$-catalyzed cross-coupling of aryl bromides with alkynes in THF. Pd(I) dimer A is demonstrated to be an active precatalyst for this reaction. ([Scheme 3.6]).

\[
\text{Scheme 3.6}
\]

CuI-catalyzed coupling reaction of aryl iodides and sulfur powder takes place in the presence of K$_2$CO$_3$ in DMF at 90 °C. The coupling mixture is directly treated with NaBH$_4$ or triphenylphosphine to afford aryl thiols in good to excellent yields. A wide range of substituted aryl thiols bearing methoxy, hydroxyl, carboxylate, amido, keto, bromo, and fluoro groups can be assembled through this procedure ([Scheme 3.7]).

\[
\text{Scheme 3.7}
\]
3.2.6. Oxidation reactions

3.2.6.1. Oxidation of allylic alcohols

Selective oxidation of allylic alcohols with chromic acid in acetone as reaction medium has been reported by K. E. Harding et. al. as shown in Scheme 3.8. \(^{11}\)

![Scheme 3.8](image)

3.2.6.2. Direct conversion of thiols to sulfonyl chlorides and sulfonamides

H₂O₂ in combination with SOCl₂ have been proved to be a, highly reactive reagent for the direct oxidative conversion of thiol derivatives to the corresponding sulfonyl chlorides with high purity through oxidative chlorination (Scheme 3.9). Upon reaction of these sulfonyl chlorides with amines in MeCN, the corresponding sulphonamides were obtained in very short reaction times. \(^{12}\)

![Scheme 3.9](image)

3.2.7. Reduction reactions

3.2.7.1. Reduction of aldehydes

The reduction of ketones and aldehydes with lanthanide metals (La, Ce, Sm, Yb) and catalytic amount of iodine (5 mol %) in \(^{1}\)PrOH proceeded smoothly to produce the corresponding alcohols as the major products in good yield, while in THF, methanol, and ethanol the pinacols were mainly produced. The yields of alcohols were improved most effectively by the use of Sm metal. (Scheme 3.10) as reported by Fukuzawa, S.-I et.al. \(^{13a}\)

![Scheme 3.10](image)
3.2.7.2. Reduction of acid chlorides

Lipshutz and co-wokers reported that exposure of functionalized aryl chlorides to catalytic quantities of nickel-on-charcoal in the presence of stoichiometric amounts of Me$_2$NH·BH$_3$/K$_2$CO$_3$ in refluxing acetonitrile leads to high yields of the dehalogenated arenes as in Scheme 3.11.$^{13b}$

$$
\begin{align*}
\text{5 mol} \% \text{ Ni/C, 0.2 eq. PPH}_3 \\
1.1 \text{ eq. Me}_2\text{NH. BH}_3, 1.1 \text{ eq. K}_2\text{CO}_3 \\
\text{Ar—Cl} & \xrightarrow{\text{CH}_3\text{CN, reflux, 5-10 h}} \text{Ar—H}
\end{align*}
$$

Scheme 3.11

3.2.7.3. Reduction of nitriles

Diisopropylaminoborane [BH$_2$N(iPr)$_2$] in the presence of a catalytic amount of lithium borohydride (LiBH$_4$) under reflux in THF, reduces a large variety of aliphatic and aromatic nitriles (Scheme 3.12). BH$_2$N(iPr)$_2$ can also reduce nitriles in the presence of unconjugated alkenes and alkynes as reported by Haddenham et. al.$^{13c}$

$$
\begin{align*}
\text{2 eq. BH}_2\text{N(iPr)}_2 \\
\text{cat. LiBH}_4 \\
\text{R—CN} & \xrightarrow{\text{THF, 25 °C or reflux}} \text{R—NH}_2
\end{align*}
$$

Scheme 3.12

3.2.8. Addition reactions

3.2.8.1. Platinum-catalyzed nucleophilic addition of vinylsilanes at the β-position

In the presence of catalytic amounts of PtCl$_2$ and metal iodides, β-substituted vinylsilanes react with aldehydes at the β-position to give allyl silyl ethers. The Pt-catalyzed addition to aromatic aldehydes proceeds efficiently in the presence of LiI in DCE as solvent. The combined use of PtCl$_2$ and MnI$_2$ was found to be effective in addition to aliphatic aldehydes as well (Scheme 3.13).$^{14a}$
3.2.8.2. Michael addition catalyzed by phosphines

C. Gimbert reported triphenylphosphine and tributylphosphine serve as excellent catalysts for Michael additions of β-dicarbonyl compounds to electron-poor olefins, including sterically demanding partners as in Scheme 3.14.\(^\text{14b}\)

\[
\begin{align*}
\text{EWG} & \quad + \quad 1.1 - 6.3 \text{ eq.} \quad \begin{array}{c}
\text{Y} \\
\text{EWG'}
\end{array} \\
& \quad \xrightarrow{0.1 - 0.2 \text{ eq.} \quad \text{Bu}_3\text{P} \text{ or Ph}_3\text{P}} \\
& \quad \text{MeCN} \\
r.\text{t. or reflux, 4 - 72 h}
\end{align*}
\]

Scheme 3.14

3.2.9. Alkylation

3.2.9.1. N-alkylation

Wang, X.-J et al. reported the bromo-directed N-2 alkylation of NH-1,2,3-Triazoles in DMF as solvent, which leads to the efficient synthesis of poly-substituted 1,2,3-Triazoles (Scheme 3.15).\(^\text{15a}\)

\[
\begin{align*}
\text{Br} & \quad + \quad \text{Br---R} \\
\text{N} \quad \text{N} \\
& \quad \xrightarrow{0.5 \text{ eq. K}_2\text{CO}_3} \\
& \quad \text{DMF} \\
-10 ^\circ\text{C or r.t., 5 - 10 h}
\end{align*}
\]

Scheme 3.15

3.2.9.2. C-alkylation

Rüping and group reported an efficient bismuth-catalyzed hydroalkylation of various styrenes, norbornene, and cyclohexadiene with 1,3-dicarbonyl compounds to give the corresponding alkylated pentanediones in good yields after short reaction times (Scheme 3.16).\(^\text{15b}\)
3.2.10. Passerini reaction

The reaction of aldehydes and ketones, including aliphatic and aromatic ones, with amides of α-isocyano-β-phenylpropionic acid in toluene as solvent in the presence of lithium bromide gives 2,4,5-trisubstituted oxazoles in good to excellent yield (Scheme 3.17).  

\[
\text{NC}R' R'' + \text{R'H} \rightarrow \text{HO}_\text{Ph} R R''
\]

Scheme 3.17

3.2.11. Enantioselective alkylative aldol reaction

The first synthetically useful catalytic alkylative aldol reaction that assembles alkylzincs, allenic esters, and unactivated ketones to afford functionalized di-lactones with a tetrasubstituted chiral center was developed by K. Oisaki et al in THF (Scheme 3.18).  

\[
\text{R} + \text{EtO} + \text{R}_2\text{Zn} \rightarrow \text{R'}_\text{(R)} - \text{DIFLUORPHOS}
\]

Scheme 3.18

3.2.12. Synthesis of (E)-α,β-unsaturated esters

α,β-Unsaturated esters were obtained with complete control of stereoselectivity utilizing a sequential reaction of dichloroesters to a variety of aldehydes, the reaction is promoted by
active manganese as shown in **Scheme 3.19**. This methodology is generally applicable, and the C-C double bond can be di- or trisubstituted.\(^{18}\)

\[
\begin{align*}
\text{R’} : & \text{H, Me, Bn} \\
\text{Mn}^* : & \\
& \text{a) 1 eq. MnCl}_2, 2 \text{ eq. LiCl, THF, r.t., 0.5 h} \\
& \text{b) 2 eq. Li, 0.3 eq. 2-Ph-pyridine} \\
& \text{THF, r.t, 1 h} \\
& \text{c) a) + b) r.t, 4 h}
\end{align*}
\]

**Scheme 3.19**

**3.2.13. Stereoselective aziridination of imines**

Tertiary amine catalyzed reaction of imines with phenacyl bromide in CH\(_3\)CN expeditiously affords functionalized aziridines in high yields and stereoselectivity by a one-pot process (**Scheme 3.20**). Advantageously, the protocol precludes the preparation and isolation of ylides and their precursors in a separate step as they are formed *in situ*.\(^{19}\)

\[
\begin{align*}
\text{R : Ar, Bu} \\
\text{DABCO :}
\end{align*}
\]

**Scheme 3.20**
3.3. Cross-conjugated dienones

3.3.1. Introduction

The number of papers dealing with the synthesis, stereochemistry and properties of cross-conjugated bis(arylmethylidene) derivatives of cyclic ketones (Figure 3.1) has considerably increased in recent years. Keen interest in these systems is associated primarily with their availability and high reactivity, making them valuable starting compounds for organic synthesis. Lately, symmetrical conjugated dienones obtained as condensation products of cyclic ketones with heteroaromatic aldehydes, have found use as exodentate ligands in the synthesis of coordination polymers. The latter hold promise in supramolecular chemistry for the design of catalytic, magnetic, luminescent, and practically important polymeric materials.

Bis(arylmethylidene) derivatives of cyclic ketones have a broad spectrum of biological activities, such as antimicrobial, androgenic, hypocholesterolemic, anti-inflammatory, antimutagenic, antitumour choleretic, and antipyretic activities. High cytotoxicity of bis(arylmethylidene)cyclohexanones and piperidin-4-ones against murine and human leukemia cells has also been documented. There is data on high antioxidant activity of hydroxybis(arylmethylidene)cyclanones, which are analogues of the natural antioxidant curcumin, and the possibility of using these compounds as insecticides, acaricides, nematocides, fungicides and herbicides. Cross-conjugated dienones find use in optics and rocket engineering where they can be used as optically active materials (for example, as sensitisers in highly sensitive composites) and as components of rocket fuels. These compounds are used also in the synthesis of polymers including those with high thermal stability (withstanding temperatures above 300°C), and in photolithography for the preparation of precision optical masks resistant to dry plasma etching.
3.3.2. Synthesis of symmetrical cyclicdienones

Symmetrical cross-conjugated dienones are generally synthesised by the aldol condensation of cyclic ketones with two equivalents of aldehydes in the presence of alkalis, alkali metal alkoxides, anhydrous potassium carbonate or magnesium hydrogensulfate (under solvent-free conditions). In a series of studies, these reactions have also been catalysed by hydrochloric acid. HCl was used in those reactions where basic catalysis is incompatible (for example, in the synthesis of hydroxyphenyl containing dienones).

Lewis acids like SOCl₂ in anhydrous ethanol, Sc(OTf)₃ and Yb(OTf)₃, silicon compounds such as Me₃Si-NaI, Me₃SiCl-NaI, (MeO)₄Si-KF, (EtO)₄Si-CsF and InCl₃·4H₂O-Me₃SiCl systems and the complex Pd-Me₃SiCl₆, zirconium compounds (Cp₂ZrH₂-NiCl₂, Cp=η⁵-C₅H₅) and titanium compounds [Cp₂TiPh₂ and TiCl₃Otf] have been used in numerous recent studies as catalysts for their synthesis. Complexes of nickel(II), cobalt(II), copper(II), and zinc(II) acetates with 2,2'-bipyridine proved to be efficient catalysts for the condensation of ketones with benzaldehyde. The catalytic properties of Lewis acids were compared in the synthesis of dibenzylidene-cyclopentanone. The highest yield of the product (93%) was achieved with the use of Yb(OTf)₃ at a concentration of 0.5 mol%-5 mol %. The aldol condensation can be performed in ionic liquids in the presence of FeCl₃ · 6H₂O or SmI₃ as the catalysts. In the presence of cationic surfactants, the condensation proceeds even in water. The products were obtained in high yields also under solvent-free conditions. These processes can be catalysed by acids, anhydrous RuCl₃ or InCl₃·4H₂O (upon heating of the reactants to 110-120 °C in a sealed tube). These reactions can also be performed using microwave activation (in the presence of boron trifluoride etherate or ethoxyphenyltellurium oxide as the catalyst; in this case, the reaction time decreases to a few minutes) or with sonication, including the reactions in the presence of KF deposited on Al₂O₃.

\[
\text{Scheme 3.21}
\]

The reactions of nitrogen-, oxygen- and sulfur-containing analogues of cyclohexanone (piperidin-4-one, tetrahydro-pyran-4-one and tetrahydrothiopyran-4-one) with aromatic and
heteroaromatic aldehydes afford 3,5-is(arylmethylidene) derivatives (ArCHO in Scheme 3.22 refers to both aromatic and heteroaromatic aldehydes). \(^{36-38,64,65,88-99}\)

Scheme 3.22

3,5-Bis(arylmethylidene)piperidin-4-ones prepared were isolated as free bases in the presence of basic catalysts \(^{51,52,92,93}\) and as the corresponding salts in the presence of acid catalysts. \(^{30,31,92,94}\)

### 3.3.3. Synthesis of unsymmetrical cyclicdienones

Unlike the well-studied symmetrical cross-conjugated dienones, their unsymmetrical analogues have received much less attention. Unsymmetrical dienones are generally synthesised by the condensation of the corresponding monoenoines with other aldehydes.

For example, the reaction of 2-arylmethylidene cycloalkanones with aromatic aldehydes in an alkaline medium produced unsymmetrical bis(arylmethylidene)cycloalka-nones. \(^{100-102}\) The reactions of derivatives containing hydroxyl or cyano groups and amidine substituents in the benzene ring were performed in the presence of acid catalysts. \(^{29,98}\)

Scheme 3.23

The synthesis of dienones containing both aryl and 1- or 2-naphthyl substituents was documented. In some reactions, the use of enamines instead of the corresponding cycloalkanones resulted in the increase in yield of the products. \(^{104}\) Dienones containing simultaneously aryl and hetaryl substituents or two different heterocycles can be synthesised by analogous reactions. \(^{50,102,105-108}\)
3.4. Present work

3.4.1. 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

Looking into the importance of cross conjugated dienones and the role of solvent in aiding the progress of reactions which are not feasible under solvent-free and other conditions, we decided to synthesize 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones (oxygen analogues of cyclohexanone), at 25 °C as they are very important group of heterocycles that have many applications in both pharmaceutical and industrial research. These bis-(arylmethylidene)-tetrahydropyran-4-ones are also used widely in bioorganic applications, and as useful and key precursors in the synthesis of a number of heterocyclic compounds. On the other hand, only a few methods are available in the literature for the synthesis of these bioactive molecules. The important methods include the reaction of tetrahydropyran-4-one or tetrahydrothiopyran-4-one with substituted benzaldehydes in the presence of catalysts such as Ba(OH)₂ in MeOH, a mixture of MgBr₂·OEt₂ and Et₃N in MeOH, LiClO₄-TMSNEt₂, HCl in AcOH, and a mixture of LiBr-Et₃N in CH₂Cl₂. However, many of these methods suffer drawbacks such as: i). Low yield of the products; ii). Require additional reagent; and iii). Take long duration for completion of the reaction.

Molecular iodine has also received considerable attention in organic synthesis as an inexpensive, easily available and environmentally benign catalyst for effecting various organic transformations. In continuation of our research program on effective utilization of simple and readily available reagents for various organic transformations and for the synthesis of biologically important compounds. We in this part, describe our finding on the formation of 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones via a double condensation reaction of araldehydes with tetrahydropyran-4-one in the presence of catalytic amount of Iodine at room temperature to get good to excellent yield of the desired products (3, Scheme 3.24).

![Scheme 3.24: 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones synthesis from araldehydes and tetrahydropyran-4-one](image_url)
Recently, we from our laboratory, have reported procedures wherein molecular iodine has been utilized as an efficient catalyst for the synthesis of azalactones, $^{117a}$ β-acetamido-β-arylpropiophenones$^{117b}$ and xanthenes.$^{117c}$

### 3.5. Results and discussion

As a preliminary study, we treated $p$-anisaldehyde (10 mmol) with tetrahydropyran-4-one (5 mmol) and catalytic iodine to get 3,5-bis-(4-methoxybenzylidene)-tetrahydropyran-4-one in DCM. To optimize the amount of iodine required for the catalytic activity 2 mmol, 1 mmol, 0.5 mmol and 0.1 mmol of iodine was employed for the purpose, and the best result was obtained with 0.1 mmol of iodine in terms of yield and reaction duration at 25 °C [95%, 60min]. In the absence of iodine, the reaction did not proceed. We next investigated the scope and generality of the reaction in which 3,5- bis-(arylmethylidene)-tetrahydropyran-4-ones (3a–3h, Table 3.1) were successfully prepared in high yield using various substituted araldehydes. In all cases, the reactions proceed rapidly and go to completion within 30–60 min at 25 °C.

**Table 3.1: Synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones from tetrahydropyran-4-one and araldehydes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (1)</th>
<th>Product (3)</th>
<th>Time (min)</th>
<th>yield (%)$^a$</th>
<th>M.P (°C)/lit.$^{113}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td></td>
<td><img src="image1" alt="Structure" /></td>
<td>30</td>
<td>98</td>
<td>186/185-187</td>
</tr>
<tr>
<td>3b</td>
<td><img src="image2" alt="Structure" /></td>
<td><img src="image3" alt="Structure" /></td>
<td>50</td>
<td>90</td>
<td>109-110/110</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image4" alt="Structure" /></td>
<td><img src="image5" alt="Structure" /></td>
<td>60</td>
<td>95</td>
<td>180/175-177</td>
</tr>
<tr>
<td>3d</td>
<td><img src="image6" alt="Structure" /></td>
<td><img src="image7" alt="Structure" /></td>
<td>55</td>
<td>85</td>
<td>169/168-170</td>
</tr>
<tr>
<td>3e</td>
<td><img src="image8" alt="Structure" /></td>
<td><img src="image9" alt="Structure" /></td>
<td>60</td>
<td>92</td>
<td>205/206-208</td>
</tr>
</tbody>
</table>
3.6. Mechanism

A plausible mechanism for the formation of 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones has been envisaged in Scheme 3.25. It is assumed that, araldehyde gets activated in the presence of iodine in the first step of the reaction. In the subsequent step condensation of the activated araldehyde with tetrahydropyran-4-one [which may exist in the enolic form] takes place to give 6, followed by elimination of a molecule of water to give the monoarylmethylidene intermediate 7 (not isolated). 7 may react with another molecule of activate araldehyde in the next step to give the product 3 as shown in Scheme 3.25.

Scheme 3.25: A plausible mechanism for the formation of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones
3.7. Experimental

All reagents were commercial and used without further purification. The products were characterized by IR, $^1$H NMR, $^{13}$C NMR and LC-MS spectral analyses. The IR and NMR spectra of the products were recorded on Shimadzu FT-IR-8400s and Bruker AMX 200-MHz spectrophotometers respectively. LC-MS was performed on an Agilent Technologies 1200 series instrument.

3.9.1 Typical procedure for the preparation of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones:

A mixture of tetrahydropyran-4-one (5 mmol), araldehyde (10 mmol) in DCM (20 ml) was stirred at 25 °C in the presence of iodine (0.1 mmol) for an appropriate time (Table 3.1). The course of the reaction was monitored by TLC [15% ethyl acetate in light petrol]. At the end of the reaction, a syrupy liquid was obtained which when allowed to stand at room temperature for 30 min gave a solid. The solid so obtained was washed with saturated Na$_2$S$_2$O$_3$ solution and dried over anhydrous MgSO$_4$ to get the crude product. The crude was subjected to purification by recrystallization from ethyl acetate.

3.8. Conclusions

In conclusion a rapid, efficient and cost-effective procedure has been developed for the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones. The procedure is simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no heating or additional equipment is required. The catalyst used is inexpensive, non-toxic, non-corrosive and readily available chemical that is commonly found in most organic chemistry laboratories. The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst-Iodine at 25°C is a remarkable feature of the procedure.
3.9. Characterisation data

(3E,5E)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a)

![Structure of (3E,5E)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a)]

Yellow crystals were obtained in 98% yield, mp 186°C (reported mp 185–187°C); IR (KBr, cm\(^{-1}\)) 1668, 1610, 1581; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.93 (d, 4H, \(J = 1.6\) Hz), 7.26–7.46 (m, 10H), 7.85 (s, 2H) ppm; \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 68.6, 128.6, 129.3, 130.4, 133.2, 134.8, 136.4, 185.5 ppm; MS: \(m/e = 277 (M^+).\)

(3E,5E)-3,5-bis(4-Methylbenzylidene)-tetrahydropyran-4-one (3b)

![Structure of (3E,5E)-3,5-bis(4-Methylbenzylidene)-tetrahydropyran-4-one (3b)]

Yellow crystals were obtained in 90% yield, mp 109–110°C (reported mp 110°C); IR (KBr, cm\(^{-1}\)) 1665, 1605, 1508, 1266; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.32 (s, 6H), 4.87 (d, 4H, \(J = 2\) Hz), 7.16 (s, 8H), 7.75 (t, 2H, \(J = 2\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.4, 68.6, 129.4, 130.7, 132.0, 132.4, 136.2, 139.7, 185.5 ppm; MS: \(m/e = 304 (M^+).\)

(3E,5E)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3c)

![Structure of (3E,5E)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3c)]

Yellow crystals were obtained in 95% yield, mp 180°C (reported mp 175–177°C); IR (KBr, cm\(^{-1}\)) 1593, 1560, 1508; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.82 (s, 6H), 4.90 (s, 4H), 7.04 (d, 4H, \(J = 8.8\) Hz), 7.41 (d, 4H, \(J = 8.8\) Hz), 7.64 (s, 2H) ppm; \(^{13}\)C NMR(CDCl\(_3\)) \(\delta\) 55.4, 68.6, 114.2, 127.6, 131.5, 132.4, 135.6, 160.6, 185.4 ppm; MS: \(m/e = 336 (M^+).\)
(3E,5E)-3,5-bis(4-Chlorobenzylidene)-tetrahydropyran-4-one (3d)

Yellow crystals were obtained in 85% yield, mp 169°C (reported mp 168–170°C); IR (KBr, cm⁻¹) 1671, 1612, 1559, 1263, 1090; ¹H NMR (CDCl₃): δ 4.80 (d, 4H, J = 2 Hz), 7.25 (d, 4H, J = 7 Hz), 7.40 (d, 4H, J = 7 Hz), 7.70 (t, 2H, J = 2 Hz) ppm; ¹³C NMR (CDCl₃) δ 68.2, 128.0, 28.8, 131.4, 133.1, 133.3, 135.0, 188.4 ppm; MS: m/e = 344 (M⁺).

(3E,5E)-Tetrahydro-3,5-bis[(E)-3-phenylallylidene]tetrahydropyran-4-one (3e)

Orange crystals were obtained in 92% yield, mp 205°C (reported mp 206–208°C); IR (KBr, cm⁻¹) 1734, 1660, 1587, 1216; ¹H NMR (CDCl₃): δ 4.77 (d, 4H, J = 2 Hz), 6.80–7.80 (m, 16H) ppm; ¹³C NMR (CDCl₃) δ 67.3, 122.0, 127.4, 127.9, 128.2, 132.2, 134.8, 137.4, 142.6, 187.2 ppm; MS: m/e = 328 (M⁺).

(3E,5E)-Tetrahydro-3,5-bis[(pyridine-3-yl)methylene]pyran-4-one (3f)

Yellow crystals were obtained in 93% yield, mp 190°C (reported mp 192–194°C); IR (KBr, cm⁻¹) 1672, 1616, 1272; ¹H NMR (CDCl₃): δ 4.86 (d, 4H, J = 2 Hz), 7.18–7.70 (m, 8H), 8.50 (br s, 2H) ppm; ¹³C NMR (CDCl₃) δ 68.2, 123.4, 130.4, 132.8, 134.6, 136.9, 149.9, 150.9, 187.0 ppm; MS: m/e = 278 (M⁺).
Chapter III

3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

\((3E,5E)-3,5\text{-bis\{Furan-2-yl\}methylene}\text{-tetrahydropyran-4-one (3g)}\)

![Chemical structure](image)

Yellow crystals were obtained in 93\% yield, mp 173°C (reported mp 170–172°C); IR (KBr, cm\(^{-1}\)) 1665, 1268, 756; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.97 (d, 4H, \(J = 2\) Hz), 6.57–6.45 (m, 4H), 7.35–7.52 (m, 4H) ppm; \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 68.4, 112.6, 117.4, 121.1, 130.1, 145.5, 151.8, 187.0 ppm; MS: \(m/e = 256 (M^+)\).

\((3E,5E)-\text{Tetrahydro-3,5\text{-bis\{thiophen-2-yl\}methylene\pyran-4-one (3h)}\)

![Chemical structure](image)

Yellow crystals were obtained in 89\% yield, mp 196°C (reported mp 195–197°C); IR (KBr, cm\(^{-1}\)) 1662, 1592, 1186; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 4.90 (d, 4H, \(J = 2\) Hz), 7.00–7.50 (m, 6H), 7.87 (br s, 2H) ppm; \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 68.3, 127.9, 128.2, 130.9, 133.3, 138.3, 184.2 ppm; MS: \(m/e = 288 (M^+)\).
Chapter III

3.5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

3.10. Selected spectra of 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

Mass spectrum of (3E,5E)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a)
Chapter III

3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

$^1$H NMR spectrum of (3E,5E)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a)
Mass spectrum of (3E,5E)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3c)
$^1H$ NMR spectrum of (3E,5E)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3c)
3.11. References


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