Synthesis and Characterization of Polymer Supported Reagents

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Abstract
There is a growing interest in chemistry of polymer supported reagents. The polymer supported reagents are used in vast majority of chemical transformation. The polymer-supported reagents are synthetic macromolecules. They have chemically bound functional groups, which may be utilized as reagents, catalysts or protecting groups in various chemical processes. So, they are also called functionalized polymers. The macromolecule can be linear or cross-linked, so called resin which though being readily solvated by a suitable solvent remains macroscopically insoluble. The concept of polymer-supported organic reactions has been of interest for more than 60 years. They began to be studied seriously in the 1940’s and early 1950’s following the commercial introduction of various organic ion-exchange resins.¹ The later were usually sulfonated cross-linked polystyrene beads (strong acid cation-exchange resins), cross-linked beads prepared using acrylic or methacrylic acids (weak acid cation-exchange resins), or cross-linked beads containing quaternary ammonium salt residues (anion exchange-resins). Typical early studies involved using resin beads bearing sulfonic acid groups as catalysts for the reactions such as sucrose inversion, alcohol dehydration, ester hydrolysis, acetalization and acetal hydrolysis.¹ So, polymer supported hypervalent iodine compounds were prepared. The hypervalent iodine compounds are used in a number of chemical transformation but the side product aryl iodide formed being soluble cannot be separated easily, but there is no such problem with hypervalent iodine compounds.

Keywords: polymer supported reagent, hypervalent iodine.

1. Introduction

The study of polymer-supported reactions received an enormous boost in 1963 when Merrifield, reported the first example of solid phase peptide synthesis.⁴ Letsinger and Mahadevan⁵,⁶ also reported the synthesis of oligonucleotide which is employed extensively today in connection with genetic engineering. The major advantage of these is that at each stage the polymer-supported oligomer is always recovered by simple filtration and washing the beads. In early 1970’s several research groups extended Merrifield and Letsinger’s methods to other areas of organic synthesis. Hodge and Sherrington have recalled many of these developments at this time in the field of polymer-supported organic reactions.³ The supported species can be a substrate, a reagent or a catalyst. Many examples of organic reactions using polymer-supported substrates, reagents, catalysts or scavengers were investigated and by 1980 approximately a thousand relevant references were available. A wide variety of supports were also investigated.⁷ The importance of correct choice of reaction solvent, the ideas of site isolation, and examples of microenvironment effects were identified, studied and substantially understood.⁸ The pros and cons of using polymer-supported substrates, reagents and catalysts were clearly recognized and various types of separation processes were developed. It was evident that reactions using polymer-supported substrates were generally least attractive of these three types. A much better way was to use polymer-supported reagents and catalysts (Scheme 1.1).

[Scheme 1.1]

Interest in the field of polymer-supported reagents/catalysts widened in recent years because of applications in combinatorial chemistry and high-throughput synthesis for pharmaceutical and agrochemical research.⁹ Polymer-supports are now extensively employed...
in the field of organic synthesis and catalysis. In recent years many new and improved solid supports has been developed in search of a cleaner, faster and more efficient route for producing new as well as compounds of biological and industrial interest. In general, the following benefits are expected when a reaction or a sequence of reactions is carried out with a polymer-supported reagent/catalyst:

(i) Ease of processing: The polymer-supported reagents are generally based on cross-linked polymer supports which are insoluble in commonly employed organic solvents. Therefore, after completion of the reaction, the unused polymeric reagent and the polymer byproduct can be easily removed from the reaction mixture by simple filtration. Further, synthesis of end-products requires minimum chromatographic steps.

(ii) Ability of the polymer to be recovered, regenerated and reused: The reaction involving functionalized polymer is designed in such a way as to allow the spent polymer by-product to be recovered quantitatively and regenerated without appreciable loss of activity (Scheme 1.2).

(iii) Ease of handling: The polymeric reagents are easier and safer to handle than their low molecular weight analogs. e.g. Aluminium chloride is a good Lewis acid catalyst, but it undergoes rapid hydrolysis by atmospheric moisture. However, the catalyst can be incorporated into polystyrene.\(^\text{10}\) The PS-AICl\(_3\) catalyst is stable towards hydrolysis and catalyzes the formation of ether (2) from dicyclopentymethanol (1) (Scheme 1.3). PS-AICl\(_3\) is also an effective catalyst for ester and acetal formation.\(^\text{11}\)

![Scheme 1.2](image_url)

In general, there are two procedures available for the preparation of polymer-supported reagents:

1. Chemical modifications of preformed polymers: Most of the work has been carried out on cross-linked polystyrene (3). The modifications of cross-linked polystyrene, besides chloromethylated polystyrene,\(^\text{4}\) includes ring brominated \((4)\)\(^\text{20}\) or ring-lithiated polystyrene \((5)\).\(^\text{21}\) The ring lithiated polystyrene resins are of particular interest due to the wide variety of otherwise inaccessible functionalities, which can be ultimately introduced. For example, ring-lithiated polystyrene can be transformed into polymer-bound phenol (6) or thiophenol \((7)\)\(^\text{20,22}\) or diphenylphosphine \((8)\).\(^\text{4}\)

![Scheme 1.3](image_url)

2. Polymerization of functional monomers: An alternate route to functional polymers is the polymerization or copolymerization of monomers, which contain the desired functionality. The number of reactive ends in the polymer chain can be reduced by addition of a co-monomer and insoluble resins are obtained in the presence of a cross-linked difunctional co-monomer. This approach has been used successfully in the preparation of polymer-supported reagent containing pyridine residues\(^\text{23}\) and benzaldehydes\(^\text{24}\) or phosphine\(^\text{20,25,26}\) units. The above facts made it clear that polymer-supported reagents and catalysts offer extensive

![Scheme 1.4](image_url)
advantages of ease of separation from the reaction mixture, lesser odour and eco-friendly nature. Further, as compared to the analogs reaction systems in solution, polymer-supported reaction can show substrate selectivity, be slower or faster, follow a different course or give a different stereocchemical result. It is also unwise to assume that a polymer-supported reaction proceeds in just the same way as the analogs reaction in the solution.

Polymer-Supported Hypervalent Iodine Reagents

Hypervalent iodine reagents have found broad applications in organic chemistry and are nowadays frequently employed in various synthetic transformations. Because these are non-metallic oxidation reagents, they avoid the issue of toxicity of many transition metals commonly involved in such processes. Synthetic use of hypervalent iodine compounds like iodobenzene diacetate (IBD, 9), has been extensively studied (Figure 1.5). These reagents carry out the reactions at mild reaction conditions and are easy to handle, resulting in high chemoselectivity and low toxicity. Based on the extensive utility of these hypervalent iodine compounds in organic synthesis, polymer-supported reagents having (diacetoxy)iodo group (PS-IBD, 12), has recently been developed (Figure 1.5).

Applications of polymer-supported hypervalent iodine reagents in organic synthesis have been widely studied and some of the key reactions of these are described herein. Polymer-supported iodobenzene diacetate (PS-IBD, 12) PS-IBD is one of the most common polymer-supported hypervalent iodine reagents serving as an excellent substitute for its low molecular analog IBD. Enolizable ketones (13) have been smoothly transformed into the corresponding α-hydroxy ketones (14) using 12 in alkaline methanol (Scheme 1.6).

\[
\begin{align*}
\text{Ar} & \quad \text{PS-IBD, NaOH} \\
& \quad \text{MeOH} \\
& \quad \text{Scheme 1.6}
\end{align*}
\]

Oxidation of saturated secondary alcohols (15) using 12 and potassium bromide in water under ultrasonic conditions proceeded in a few hours to give the corresponding ketones in good yield, whereas, primary alcohols were converted to carboxylic acids (Scheme 1.7).

\[
\begin{align*}
\text{R-} & \quad \text{PS-IBD, KBr} \\
& \quad \text{H}_2\text{O}, \text{ r.f.} \\
& \quad \text{Ketones or Carboxylic acids} \\
& \quad \text{Scheme 1.7}
\end{align*}
\]

PS-IBD has been efficiently utilized in producing a variety of heterocycles. A facile synthesis of 3,5-disubstituted-1,2,4-thiadiazoles (17) have been achieved using 12 by oxidative dimerization of the corresponding thioamides (16) on stirring for 5-10 min in dichloromethane (Scheme 1.8).

\[
\begin{align*}
\text{S} & \quad \text{PS-IBD, DCM} \\
& \quad \text{Ar-NH}_2 \quad \text{stir} \\
& \quad \text{Ar} \quad \text{S-N} \quad \text{Ar} \\
& \quad \text{Ar} = \text{C}_9\text{H}_6, 4-\text{CH}_3\text{OC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, \\
& \quad \text{Scheme 1.8}
\end{align*}
\]

II. Results and Discussion

In the past, hypervalent iodine compounds have been used extensively for a variety of chemical transformations and particularly as reagents in several oxidation reactions. Whenever a hypervalent iodine compound is employed in chemical transformation, it produces aryl iodide as side product after the completion of the reaction. The aryl iodides, being liquids, are difficult to remove from the reaction mixture and often it requires some tedious chromatographic steps in order to obtain the desired pure product. The polymer-supported hypervalent iodine reagents have been developed which avoids the removal of aryl...
iodide, as iodopolystyrene, being insoluble in the commonly employed organic solvents, can be easily removed from the reaction mixture just by filtration. The polymer-supported hypervalent iodine reagents were synthesized using commercially available 2% divinylbenzene cross-linked polystyrene. Its main advantages are: a) good mechanical stability and well defined physical characteristics, (b) the aliphatic backbone of the polymer is unreactive and thus the polymer is not susceptible to degradative chain scission and (c) the aromatic rings are very reactive that can be easily functionalized. The microenvironment in the vicinity of the polymer backbone is expected to be sterically crowded. Therefore, the reaction at the phenyl residues of polystyrene occurs mainly at the meta- and para-position and not the ortho-position. In general, steric effect will be greatest when a reactive functional group is directly attached to the polymer backbone, but as the functional groups are separated from the backbone by spacer groups, steric effect would be expected to disappear rapidly and functional group accessibility and mobility may increase. In case of polystyrene the benzene ring itself will act as a small rigid spacer group. In the present study, 2% cross-linked polystyrene (10) was firstly iodinated with molecular iodine, iodine pentaoxide and sulfuric acid on refluxing in a mixture of nitrobenzene and carbon tetrachloride for 24 h to produce iodopolystyrene (PS-I). PS-I was quantitatively acetoxylated with peracetic acid generated in situ from a stirred solution of acetic anhydride and 30% hydrogen peroxide to afford polymer-supported iodobenzene diacetate (PS-IBD, 12) in excellent yield. It may also be called as polystyrene-supported iodobenzene diacetate or polystyrene-supported diacetoxyiodobenzene (PS-DIB). PS-IBD (12) is the key precursor to furnish other polymer-supported hypervalent iodine reagents on treatment with suitable reagents in good yield (Scheme 1.9).

The synthesized polymer-supported hypervalent iodine reagents were characterized using physical methods as well as IR and thermal studies [differential scanning calorimetry (DSC) and thermogravimetry (TG)]. However, NMR spectra could not be recorded due to solubility problem. All the polymer-supported hypervalent iodine reagents (PS-IBD) showed the presence of C-H stretching and aromatic ring stretching bands. The carbonyl stretching bands in PS-IBD observed at 1650. Thermal behavior of hypervalent iodine reagents and polymer-supported hypervalent iodine reagents (PS-IBD) including that of polystyrene and iodopolystyrene was investigated by TG and DSC. TG is the branch of thermal analysis which examines the mass of a sample as a function of temperature. It is used to characterize the decomposition and thermal stability of materials. TG curves are plotted with the mass change expressed as percentage on the vertical axis and temperature on the horizontal axis. From TG traces, the initial decomposition temperature (IDT), the final decomposition temperature (FDT) and temperature at which the weight loss was maximum (T_{max}) is reported. IDT at which the sample starts decomposing was obtained by extrapolation with the steep portion of weight loss curve and initial base line. FDT is the temperature at which the weight loss completes: it was also obtained by extrapolation. It was summarized that hypervalent iodine reagents were stable up to 132-160°C and polymer-supported hypervalent iodine reagents were stable up to 398-410°C and significant loss occurred after this temperature. These results suggest that polymer-supported hypervalent iodine reagents may be utilized in high boiling solvent without decomposition up to 398°C. TG data are presented in Table 1.1.
Table 1.1 TG analysis of hypervalent iodine reagent and polymer-supported hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>IDT (°C)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (°C)</th>
<th>HDT (°C)</th>
<th>Wt. lost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>310</td>
<td>375</td>
<td>420</td>
<td>97</td>
</tr>
<tr>
<td>PS-I</td>
<td>305</td>
<td>372</td>
<td>410</td>
<td>95</td>
</tr>
<tr>
<td>IBD</td>
<td>154</td>
<td>178</td>
<td>205</td>
<td>97</td>
</tr>
<tr>
<td>PS-IBD</td>
<td>337</td>
<td>380</td>
<td>398</td>
<td>95</td>
</tr>
</tbody>
</table>

DSC study indicated that there was appearance of an endotherm at the melting temperature of hypervalent iodine reagent followed by an exotherm. The area under the exotherm (or endotherm) is related to the value of enthalpy change (ΔH). However, in case of polymer-supported hypervalent iodine reagents, there was no endotherm; rather exotherms were obtained. The enthalpy change along with peak temperature and onset temperature are gathered in Table 1.2. endotherm at the melting temperature of hypervalent iodine reagents followed by an exotherm.

Table 1.2 DSC analysis of hypervalent iodine reagent and polymer-supported hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Peak Temp. (°C)</th>
<th>Onset Temp. (°C)</th>
<th>Enthalpy ΔH J/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>262.86</td>
<td>229.13</td>
<td>155.1</td>
</tr>
<tr>
<td></td>
<td>401.04</td>
<td>337.88</td>
<td>301.4</td>
</tr>
<tr>
<td>PS-I</td>
<td>307.73</td>
<td>286.93</td>
<td>62.86</td>
</tr>
<tr>
<td></td>
<td>388.17</td>
<td>369.74</td>
<td>143.0</td>
</tr>
<tr>
<td>IBD</td>
<td>161.14</td>
<td>153.14</td>
<td>85.75</td>
</tr>
<tr>
<td></td>
<td>188.94</td>
<td>174.58</td>
<td>266.7</td>
</tr>
<tr>
<td>PS-IBD</td>
<td>157.99</td>
<td>123.27</td>
<td>136.5</td>
</tr>
<tr>
<td></td>
<td>390.42</td>
<td>371.33</td>
<td>164.2</td>
</tr>
</tbody>
</table>

Regeneration and recycling PS-IBD (12) was also studied. After completion of reaction, iodopolystyrene (11) was recovered by filtration followed by washing with methanol. The recovered iodopolystyrene was then reoxidized with peracetic acid. The activity of regenerated PS-IBD was almost the same as before, as evidenced by similar reaction time and yield.

III. Experimental Procedure

Synthesis of PS-I (11)

A mixture of 2% cross-linked polystyrene (9 g), iodine (11 g, 37 mmol), iodine pentoxide (5 g, 21.0 mmol) in 25 mL of carbon tetrachloride and 20 mL of 50% sulfuric acid in 100 mL of nitrobenzene in a round bottomed flask was stirred at 90°C in an oil bath for 60 h. The reaction mixture was diluted with 50 mL of chloroform followed by the addition of methanol (100 mL) to precipitate out iodopolystyrene (11) that was collected by filtration and dried. IR (KBr, cm⁻¹): 3024 (CH), 3001 (CH), 2922, 2850, 1598, 1583, 1523, 1477, 1444, 1402, 1344, 1180, 1153, 1001, 812, 744, 680.

Synthesis of PS-IBD (12)

Hydrogen peroxide (30%, 45 mL) was added drop wise to acetic anhydride (150 mL) in a round bottom flask at 0°C. The solution was slowly warmed to room temperature and stirred overnight followed by addition of iodopolystyrene (9 g). Then the reaction mixture was stirred overnight. After completion of the reaction, diethyl ether was added to cause precipitation. PS-IBD (12) so precipitated was collected by filtration and dried. IR (KBr, cm⁻¹): 3010 (CH), 2920 (CH), 2852, 1650 (CO), 1492, 1361, 1234, 1153, 1000, 770.

References
