Synthesis and Characterization of Polymer-Bound Anthranilic Acid

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Synthesis of Polymer Supported Anthranilic Acid

Introduction

Selective oxidation of a primary alcohol to the corresponding aldehyde is a transformation of paramount importance in synthetic organic chemistry as well as in bioorganic chemistry. While NAD$^+$ and NADP$^+$ perform this selective transformation efficiently under biological conditions, same cannot be said to be true for the plethora of reagents presently available in synthetic organic chemistry. The selective oxidizing agent should be able to recognize between primary and secondary alcohols and as well should not affect other sensitive functional groups present elsewhere in the molecule. Moreover the oxidizing agent should stop the oxidation at aldehyde stage itself and not cause further transformation to carboxylic acid.

Many oxidizing agents based on chromium, manganese and ruthenium are widely used for the oxidation of an alcohol to the corresponding carbonyl compound. However, these reagents, apart from lack of selectivity, generate toxic byproducts. Furthermore, several non-metal based oxidizing agents require additional reagents and demand stringent experimental conditions. Non-metal based oxidizing agents such as DMSO, bromine, nitric acid, potassium bromate and potassium chlorate are widely used. However, lack of selectivity, slow rate of oxidation and necessity of fine turning of the conditions for general applicability are some of the problems associated with non-metal based oxidizing agents.

In 1983, Dess and Martin introduced periodinane based oxidizing agent 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1, now commonly known as Dess-
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Martin Periodinane (DMP) as a convenient and selective oxidizing agent. DMP causes selective oxidation of a primary alcohol to aldehyde. Oxidation of a secondary alcohol to ketone is very slow and therefore selective oxidation of primary alcohol in the presence of secondary alcohol can be achieved. Due to near neutrality of the reagent and the byproducts, DMP tolerates several acid sensitive functional groups. For example, oxidation of a primary alcohol present in the carbohydrate substrate having acetal, epoxide or allyl ethers elsewhere in the molecule was found to be intact while performing oxidation with DMP. However, DMP is air sensitive, therefore, it has to be prepared in situ or stored under inert conditions. The precursor to DMP is 1-hydroxy-1,2-benziodoxol-(1H)-one-1-oxide (IBX). IBX is a stable white solid and shows high degree of selectivity towards the oxidation of a primary alcohol to corresponding aldehyde. Major drawback of IBX is its solubility. The reagent is sparingly soluble in common solvents such as dichloromethane, chloroform, etc. However, Corey and coworkers discovered that DMSO could be used as a convenient solvent for IBX assisted oxidation reactions. Other drawback of IBX is that it is heat and pressure sensitive. IBX was found to explode on heating to its high temperature and therefore utility of the reagent is restricted. We reasoned that when IBX was installed on a polymer matrix the reagent could be more useful due to suppression of explosive characteristics. Since the byproduct of IBX assisted oxidation reaction is 2-iodobenzoic acid, which can be recycled for the regeneration of IBX. The regeneration of IBX is more facile if it is polymer-bound. Therefore we targeted the synthesis of polymer-bound IBX.
While our work was in progress three groups have independently published the synthesis of solid-supported IBX and demonstrated the utility of the reagent for selective oxidation of primary alcohols. However, there is still scope for the development of process this useful polymer-bound reagent. In the following we describe our efforts towards the synthesis of polystyrene-bound IBX. In this effort we have succeeded in the synthesis of polymer-bound anthranilic acid.

Results and Discussion

Retro-synthetic analysis for polymer-bound IBX 3 is given in Fig. 2. Immediate precursor for polymer-bound IBX 3 is polymer-bound 2-iodobenzoic acid 4. The polymer-bound 2-iodobenzoic acid 4 can be prepared from polymer-bound anthranilic acid 5 via diazotization and exchange with the diazo group with iodide ion. Polymer-bound anthranilic acid 5 can be generated from polymer-bound 2-nitrobenzoic acid 6. Polymer-bound 2-nitrobenzoic acid 6 can be prepared from polymer-bound 2-nitrobenzyl chloride 7, which in turn could be generated from Merrifield resin 8.
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Synthesis of polymer-bound anthranilic acid 5 is given in Scheme 1. We prepared cross-linked polystyrene from styrene and 2% divinyl benzene following the literature procedure.\(^7\) The polystyrene was chloromethylated with methoxymethyl chloride in presence of catalytic quantity of titanium (IV) chloride following the procedure described by Merrifield.\(^7\) Nitration of Merrifield resin with the nitrating mixture of concentrated sulfuric acid and concentrated nitric acid resulted in polymer-bound 2-nitrobenzyl chloride 7.\(^7\) The nitration was confirmed on the basis of IR spectrum, which showed characteristic peaks at 1522 and 1345 cm\(^{-1}\) (Fig. 3). Oxidation of chloromethyl group was carried out with conc. nitric acid. The IR spectrum of this material revealed the appearance of the carbonyl group of the acid and disappearance of chloromethyl functionality (Fig 3). Reduction of the nitro group to amino group using tin (II) chloride, hydrochloric acid in methanol was uneventful for the generation of polymer-bound anthranilic acid 5. Signals due to nitro group disappeared and the new signals due to amino appeared in the spectrum (Fig 3).
Next, we made several unsuccessful attempts to get diazotized amine 5 to the corresponding iodo compound 6. However, in spite of best efforts we could not succeed in the conversion of polymer-bound anthranilic acid 5 to polymer-bound 2-iodobenzoic acid 4, even though the transformation works well on isolated molecules. We have used well-accepted conditions such as sodium nitrite in dilute hydrochloric acid at 0 °C, sodium nitrite in dilute sulfuric acid at 0 °C, amyl nitrite at 0 °C etc. Possible explanation is as follows: Polymer-bound anthranilic acid 5 is very close to the backbone and therefore unapproachable, or the anthranilic acid 5 unit is getting diazotized but diazo group is not getting displaced.

Polymer-bound anthranilic acid 5 itself is an important material due to its amino acid type structure. In future, we plan to use this polymer to synthesize some polymer-bound heterocycles exhibiting unusual properties.

Conclusion

We have prepared polymer-bound anthranilic acid from polystyrene via four-step functional group transformation.
Fig. 3 The IR spectra in the synthesis of polymer-bound anthranilic acid (5)
Experimental Section

All reagents and solvents were purchased from SD'S, E-Merck and Sisco Chemicals, India. The IR spectra were recorded as KBr pellets using Bomem MB104 spectrometer.

Synthesis of polystyrene. In a 1000 mL RB flask, the monomer mixture [styrene (49 g), divinylbenzene (1 g) and dibenzoyl peroxide (0.25 g)] was added drop by drop to the solution of polyvinyl alcohol (1.0 g) in distilled water (500 mL) at 80 °C for 12 h. The polymer beads were filtered at hot condition, washed with hot water and dried. The polymer beads were purified by washing with 1 M NaOH, 1 M HCl, distilled water, methanol and dried. Yield: 47 g. IR: 3027, 2920, 1605.

Chloromethylation of the polystyrene (8). In a 100 mL RB flask, the polystyrene-(2%) divinylbenzene copolymer (5 g) was swelled in chloroform (45 mL) at room temperature for one hour and then cooled to 0 °C. A cold solution of anhydrous titanium tetrachloride (1.5 mL) in chloromethyl methylether (5 mL) was added and stirred for 30 min at 0 °C. The greenish-white polymer was filtered, washed with 3:1 dioxane-water, 3:1 dioxane-3N HCl, water and finally washed with methanol. Yield: 5 g. The product contained 0.83 mmol of Cl/g. IR: 3022, 2920, 1605, 825.

Nitration of the polymer (7). A 100 mL RB flask was charged with the chloromethylated polymer 8 (5 g) and nitrating mixture (4.5 mL conc. HNO₃ and 10.7 mL conc. H₂SO₄) and stirred at 0 °C for 30 min and the temperature was raised to 60 °C for 30 min. The resulting mixture was allowed to cool to room temperature and poured into crushed ice. The light tan beads were filtered, washed with dioxane-water, 3:1 dioxane-3N HCl, water and finally washed with methanol. Yield: 5.7 g. IR: 2923, 1623, 1522, 1345.
Oxidation of the polymer (6). In a 50 mL RB flask, the nitrochloromethylated polymer 7 (5 g) was added slowly to the concentrated nitric acid (10 mL) and refluxed for 5 h. The contents were cooled to room temperature. The polymer product was filtered, washed with water and dried. Yield: 5 g.

IR: 3433, 2922, 1699, 1606, 1520, 1346.

Reduction of the polymer (5). A 100 mL RB flask was charged with polymer 6 (7 g), tin (II) chloride (15 g), methanol (70 mL) and conc. HCl (3.5 mL). The reaction mixture was refluxed for 3 h and cooled to room temperature. The reaction was monitored by IR spectroscopy. The resulting polymer 5 was filtered, washed with water and dried. Yield: 7 g.

IR: 3410, 2919, 1699, 1606.

References


