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Rate intensive and selective etherification of vanillin with benzyl chloride under solid–liquid phase transfer catalysis by aqueous omega phase

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Abstract

The alkylation of vanillin, containing three reactive groups, with benzyl chloride is challenging and can lead to both C- and O-alkylated products, particularly when liquid–liquid (L–L) phase transfer catalysis (PTC) is used. In the current studies, solid–liquid (S–L) PTC has been employed in the reaction of solid sodium salt of vanillin and benzyl chloride in toluene at 90 °C to make 4-benzyloxy vanillin, an ether, which is used as a perfume and also as a starting material for the synthesis of thalifoline, ephedradine as alkaloids and in synthesis of flavonoid compounds. The selectivity towards the desired product under S–L PTC is 100%. The rates of reaction are enhanced greatly by using trace quantities of water (the so-called omega phase (ω)) with 100% selectivity to the ether. Efficacy of various phase transfer agents such as TBAB (tetra-*n*-butyl ammonium bromide), TBAHS (tetra-*n*-butyl ammonium hydrogen sulfate), TPAB (tetra-*n*-propyl ammonium bromide), TEAB (tetraethyl ammonium bromide) and ETPB (ethyl triphenyl phosphonium bromide) was evaluated under otherwise similar conditions at 90 °C and explained. The order of activity was as follows: TBAB (maximum) > TBHS > TPAB > TEAB > ETPB (minimum). A theoretical model is developed to account for the enhancements in rates of reaction and selectivity to the ether. The kinetic constants have been evaluated and the apparent activation energy is determined as 9.64 kcal/mol. The results are novel.

Keywords: Solid–liquid phase transfer catalysis; Aqueous omega phase; Vanillin; Benzyl chloride; 4-Benzyloxy vanillin; Etherification; Kinetics; Selectivity

1. Introduction

Phase transfer catalysis (PTC) has matured into a beneficial industrial practice for the past three and half decades [1,2]. A repertoire of reactions with complex mechanisms and kinetics has been pursued and over 600 odd examples are cited, amongst which alkylation and polymerization constitute a majority. The major advantages of PTC include high yield, high reaction rate, and selectivity to the desired product with less quantity of catalyst, mild conditions and reduction in energy consumption. Various strategies by which PTC can be converted into a green concept have been recently highlighted [3]. Alkylation reactions present a challenging selectivity problem in PTC, wherein different functional groups such as OH, SH, NH_2 and CH_2 are present in the same substrate leading to different products having several applications. Preparation of substituted aromatic ethers is one such example, which is amenable to PTC.

Williamson synthesis is the most widely used route for the synthesis of substituted aromatic ethers. Although the normal method involves treatment of a halide with an alkoxide, it is also possible to mix the halide and alcohol directly with solid KOH and DMSO [4] or with HgO and tetrafluroboric acid in CH_2Cl_2 [5]. Yadav et al. [6–13] have developed several new beneficial PTC procedures for Williamson synthesis in terms of mildness of conditions, yield, and convenience including liquid–liquid (L–L), solid–liquid (S–L) and liquid–liquid–liquid (L–L–L) PTC in the presence of microwave irradiation, named as MILL-PTC, MISL-PTC and MILLL-PTC, respectively [14–18].

A large number of industrially important reactions involve the use of PTC under liquid–liquid conditions [1,2]. The major disadvantage of L–L PTC is that the catalyst remains distributed between the two-liquid phases and it cannot be recovered easily and due to presence of water it can lead to side reactions such as hydrolysis and oxidation in substituted phenolic compounds. To overcome this problem the conversion of an L–L PTC reaction in to a solid–organic liquid reaction proves to be favourable from the perspective of not only suppression of different types of side reaction but also the intensification of rates and selectivity to the

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Nomenclature

$[Y^-]_\omega$	concentration of Y^- in the ω phase (mol/cm^3)
$[QX]_\omega$	concentration of QX in ω phase (mol/cm^3)
$[QX]_{org}$	concentration of QX in organic phase (mol/cm^3)
$[X^-]_\omega$	concentration of X^- in ω phase (mol/cm^3)
$[QY]_\omega$	concentration of QY in ω phase (mol/cm^3)
$[RX]_{org}$	concentration of RX in the organic phase (mol/cm^3)
$N_{Q\,total}$	feed mole of catalyst (mol)
$N_{Q\text{-}\omega}$	moles of catalyst in omega phase (mol)
$N_{Q\text{-}org}$	moles of catalyst in organic phase (mol)
$N_{QX\text{-}\omega}$	moles of QX in omega phase (mol)
$N_{QY\text{-}org}$	moles of QY in organic phase (mol)
$N_{QX\text{-}org}$	moles of QX in organic phase
$N_{QY\text{-}\omega}$	moles of QY in omega phase (mol)
k_{R_2}	second order rate constant ($cm^3\,mol^{-1}\,min^{-1}$)

desired product. The rates are enhanced due to the increase in particle surface area by orders of magnitude in comparison to that offered in liquid–liquid dispersion. Furthermore, in a S–L PTC process, addition of a third aqueous phase in trace amounts to form the so-called omega phase (ω) enhances the rates and selectivity to a great extent [19–23]. While several papers have been written on the advantages of S–L PTC in several types of reactions [1–3,24–27], there is a dearth of studies on the modeling aspects [28–30].

The current work focuses on the novelties of etherification of vanillin with benzyl chloride under S (reagent)–L (aqueous ω phase) and L (organic reagent) PTC process over L–L PTC to get 4-benzyloxy vanillin selectively which is an important product in perfumery industries. The product is also used as a starting material for synthesis of thalifoline, ephedradine as alkaloids and in synthesis of flavonoid compounds [31,32]. Besides, vanillin is an ideal substrate containing hydroxyl, aldehyde and ether groups, in which only the O-alkylation without attacking any other groups is targeted. The current paper covers the determination of process parameters such as catalyst structure, catalyst loading, substrate loading, and temperature on the conversion and rates of reaction. The role of omega (ω) phase, in the intensification of rate and selectivity is investigated.

2. Experimental

2.1. Chemicals and catalysts

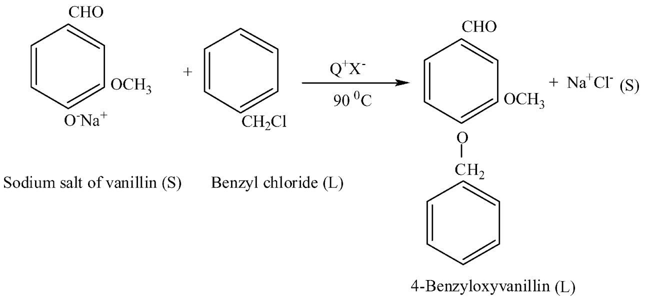
Benzyl chloride, vanillin, toluene and sodium hydroxide all of AR grade were obtained from M/s s.d. Fine Chemicals Pvt. Ltd. Mumbai, India. TBAB (tetra-*n*-butyl ammonium bromide), TEAB (tetraethyl ammonium bromide), TPAB (tetra-*n*-propyl ammonium bromide), ETPB (ethyl triphenyl phosphonium bromide) and TBAHS (tetra-*n*-butyl ammonium hydrogen sulfate) of pure grade were procured as gift samples from M/s. Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India. These were used as received without any further purification. All other chemicals were of analytical grade.

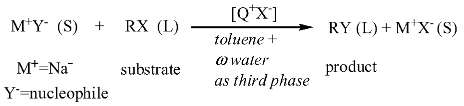
2.2. Experimental set-up

The reactions were studied in a 5.0 cm i.d. fully baffled mechanically agitated contactor of 100 cm^3 total capacity, which was equipped with a six-blade-turbine impeller (1.7 cm diameter) and a reflux condenser. The reactor was kept in an isothermal bath whose temperature could be maintained at the desired value using a temperature indicator controller. Typical runs were conducted by taking 3 g vanillin as fine solid particles (0.02 mol), 0.97 g dry NaOH (0.02425 mol) and 30 ml toluene. It was agitated at 1200 rpm at 110 °C for 1 h to ensure complete formation of the sodium salt of vanillin. Then the temperature was reduced to 90 °C. The reaction mass contained 0.36 ml water, which was miscible in the toluene phase. The reaction mass contained fine slurry of sodium vanillinate. To this slurry, 0.02 mol benzyl chloride and 1 ml of water (ω phase) and 0.002 mol phase transfer catalyst were added. A zero time sample was withdrawn. All the typical reactions were carried out at 90 °C and 1200 rpm. The reaction scheme is as given below.

2.3. Analysis and isolation of product

Samples were withdrawn periodically and analyzed by GC (Chemito Model 8610) by using a stainless steel column (3.25 mm × 4 m) packed with a liquid stationary phase of 10% OV-17. The conversion was based on the disappearance of benzyl chloride in the organic phase. At the end of the reaction, the reaction mass which contained 4-benzyloxy vanillin was washed with water to remove any traces of catalyst, sodium salt of vanillin, and the solvent was distilled under vacuum to get pure solid product. The melting point of isolated 4-benzyloxy vanillin (99.0% purity) was found to be 63–64 °C (literature value 61–64 °C). It was also confirmed by GC–MS. A complete material balance was also done. There was no side product in this reaction.





$$\underset{\substack{M^+=Na^-\\ Y^-=\text{nucleophile}}}{M^+Y^-\ (S)} + \underset{\text{substrate}}{RX\ (L)} \xrightarrow[\substack{toluene\ +\\ \omega\ water\\ as\ third\ phase}]{[Q^+X^-]} \underset{\text{product}}{RY\ (L) + M^+X^-\ (S)}$$

A general mechanism for the reaction and mode of operation is shown in Fig. 1, which involves the dissolution of solid M^+Y^- (sodium vanillate) in to the aqueous ω phase, followed by anion-exchange reaction with the catalyst to form the