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Full Length Research Paper

Convergent preparation of 2-phenylethanol

Alofoje Unuigboje* and Bright Emenike

Department of Chemistry, Federal University of Technology, Owerri, Imo State, Nigeria.

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The convergent synthesis of 2-phenylethanol was executed with bromination of benzene in the presence of pyridine to give bromobenzene which was reacted with magnesium metal to give phenylmagnesium bromide. Ethene was generated from ethanol and converted to 1,2-dibromoethane which in turn was reacted with the Grignard in an inverse manner to give 2-phenylbromoethane. Reaction of 2-phenylbromoethane and aqueous sodium hydroxide, in acetone as solvent, yielded 2-phenylethanol.

Key words: 2-Phenylethanol, 1,2-dibromoethane, 2-phenylbromoethane.

INTRODUCTION

Flavour is usually the result of the presence of many volatile and non-volatile compounds, possessing diverse chemical and physicochemical properties. While the non-volatile compounds contribute mainly to taste, the volatile ones influence both taste and aroma (Longo and Sanroman, 2006). A multitude of compounds may be responsible for the aroma of food products – alcohols, aldehydes, esters, dicarbonyls, short to medium chain free fatty acids, methyl ketones, lactones, phenolics and sulphur compounds (Urbach, 1997; Gatfield, 1988).

Since early times, flavour compounds have been extracted from plant sources. Some problems associated with direct extraction are, low concentration of the desired compounds, among a myriad of other compounds, making separation and hence the extraction/recovery process expensive. Moreover, the use of compounds so derived, depend on factors that are difficult to control, such as weather and plant diseases.

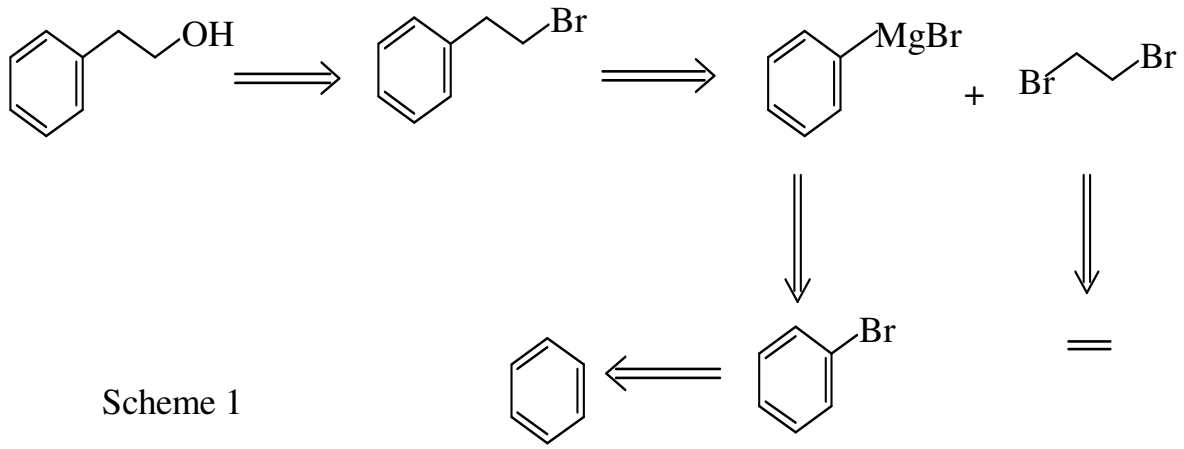
Plant cell cultures may serve as a method to produce a wide range of flavours and aromas (Kim et al., 2001; Drawert et al., 1984; Suvamalatha et al., 1994; Townsley, 1972; Nakao et al., 1999; Ohsumi et al., 1993; Nabeta et al., 1983; Prince et al., 1997; Ayabe et al., 1990; Domenburg and Knorr, 1996), by virtue of their biochemical and genetic capacity and the totipotency of plant cells (Harlander, 1994; Sahai, 1994; Scragg, 1997). However, the technology for large scale suspension cultures differ from that employed for microbial systems. Sensitivity to shear stress, relatively long growth cycles, low yields, progressive loss of biosynthetic activity and rare product secretions, are some of the disadvantages.

The compound 2-phenylethanol is a primary aromatic alcohol which is permitted for direct addition to food for human consumption as flavouring substances. The essential oil from *Pandamus* flower consists of 32% 2-phenylethanol. It is used in fragrance in a wide variety of consumer products such as colognes, cosmetic soaps and detergents, because of its characteristic rose-like odour. It exhibits bacteriostatic properties and finds use as a preservative and disinfectant. When ingested, 2-phenylethanol is oxidized to phenylacetic acid, which is consequently excreted in the urine. The dearth of locally produced flavours necessitated this work. Various methods have been employed in the synthesis of 2-phenylethanol. These include Friedel-Crafts reaction of benzene and oxirane with $AlCl_3$ as catalyst, hydrogenation of styrene oxide with Raney Nickel, and metal reduction of ethyl-2-phenylacetate (Nomura et al., 2001; Popper et al., 1961).

While natural 2-phenylethanol is extracted mainly from rose petals, through a high-cost process (Fabre et al., 1994), various yeast strains have shown potential for its production (Stark et al., 2002, 2003).

Given the paucity of materials and equipment in our setting, the synthesis of 2-phenylethanol was approached from a fundamental retrosynthetic standpoint, whose synthons were readily available or capable of being synthesized. Scheme 1 outlines the retrosynthesis, which

*Corresponding author. E-mail: Chemafric@yahoo.com.



Scheme 1. Retrosynthesis of 2-phenylethanol.

revealed benzene and ethanol as basic synthons.

EXPERIMENTAL

All boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer IR-237. The ^{1}H NMR spectra were taken on a Varian EM 360 instrument and are reported in parts per million downfield from TMS as internal standard.

Bromine

To 200 g (1.9 m) of NaBr, 87 g (1.0 m) of MnO_2, taken in a 250 ml round-bottom flask equipped with a thistle funnel, that dipped to the bottom of the flask and a delivery tube leading into a water-cooled condenser, that was connected to a receiver immersed in an ice-bath, was dripped a total of 200 g (2.0 m) of conc. H_2SO_4, with heating over a period of 2 h. The apparatus was filled with the reddish-brown bromine, which condensed in the receiver, while HBr was exhausted into the fume chamber. Yield was 50 g (64%).

Bromobenzene

To 50 g (1.64 m) of dry benzene taken in a 250 ml round-bottom flask immersed in a cold-water bath, was added 125 g (1.56 m) of Br_2. After the initial vigorous reaction subsided, the reaction was warmed to 25 to 30°C for 1 h, followed by temperature increase to 65 to 70°C for a further 45 min. At this point, Br_2 had disappeared and the evolution of HBr had ceased. The dark-coloured reaction mixture, was transferred into a separatory funnel and washed with 2 x 50 ml of H_2O. The product was dried over anhydrous $MgSO_4$ and then distilled twice – first at 150 to 170°C followed by redistillation at 154 to 157°C to to give 65.3 g (65%). 1H NMR (CDCl3) 7.23 to 7.20 (d).

Phenylmagnesium bromide

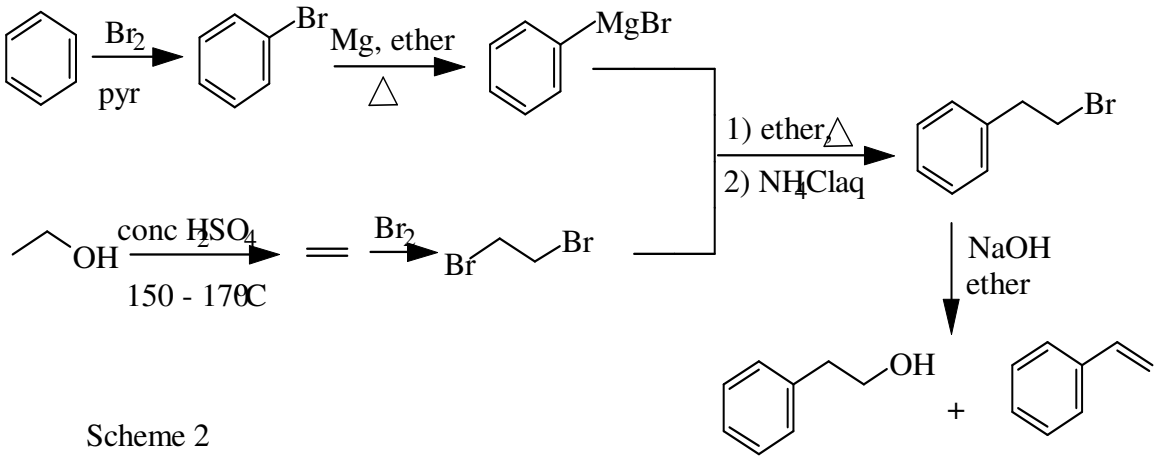
Magnesium ribbon (6.2, 0.26 g, at.) cut up into little bits and 40 ml of anhydrous diethyl ether were taken in a 250 ml 3-necked round-bottom flask, equipped with a dropping funnel with a pressure-equalizing arm and a reflux condenser, carrying a drying tube. In the dropping funnel was placed 39 g (0.25 m) of bromobenzene in 60 ml of anhydrous diethyl ether. A few drops of diethyl ether were dripped into the reaction followed by warming and stirring. Lack of reaction necessitated addition of a crystal of iodine which initiated the reaction. The remaining bromobenzene was then added dropwise over 2 min in such a manner as to maintain gentle refluxing, followed by further refluxing in a hot-water bath for additional 30 min.

1,2-Dibromoethane

To 35 ml (0.43 m) of absolute ethanol taken in a 150 ml round-bottom flask was added 42 g of conc. H_2SO_4. One neck of the flask carried a thermometer that dipped into the reaction mixture while the second carried a delivery tube leading to a bottle trap, which in turn was connected by another delivery tube which dipped into the bottom of 10 ml (0.39 m) of bromine in water contained in a 100 ml round-bottom flask. The third neck of the flask was stoppered. The reaction was heated in an oil-bath maintained at 150 to 170°C. A positive ethene pressure developed with occasional bubble, until the reddish-brown colour of bromine was discharged. The lower organic phase was separated from the clear upper aqueous phase, washed with 2 x 10 ml of H_2O, dried over anhydrous Na_2SO_4 and distilled, giving 58 g (80%) of sweet-smelling distillate at 130 to 134°C. ^{1}H NMR

2-Phenylethyl bromide

The previously prepared Grignard was transferred to a dropping funnel. The dropping funnel was connected to one neck of a 3-necked 250 ml round-bottom flask with the second neck carrying a condenser with a drying tube, while the third neck was stoppered into the 250 ml round-bottom flask was placed 58 g (0.31 m) of 1,2-dibromoethane and 60 ml of dry diethyl ether. While refluxing in a water-bath, the phenylmagnesium bromide was added dropwise with stirring, over a 30 min period. Reaction was allowed to cool to room temperature and 6 M HCl was added dropwise until it tested acidic to pH paper. Reaction was transferred to a separatory funnel and the upper organic phase collected while the aqueous organic phase was extracted with 2 x 20 ml of diethyl ether. The organic phases were combined, washed with 20 ml of H_2O and then dried over anhydrous $MgSO_4$, followed by distillation of the decantate upto a temperature of 140°C to remove much of the diethyl ether



Scheme 2. Synthetic pathway to 2-phenylethanol.

and unreacted 1,2-dibromoethane. ^{1}H NMR ($CDCl_3$) 6.74, 2.31 (t), 2.35 (t).

2-Phenylethanol

To the crude 2-phenylethyl bromide was added to 30 ml of acetone and 12 g of NaOH dissolved in 15 ml of H_2O. The reaction was refluxed for 1 h, allowed to cool to room temperature and quenched by pouring into 100 ml of cold water. The quench was extracted with 2 x 50 ml of diethyl ether, washed with 50 ml of water and dried over anhydrous Na_2SO_4. Distillation at 210 to 220°C gave 14.2 g of product (37% based on Grignard) IR (Nujol) cm^{-1}; 3215 to 3400 (-OH broad band), 2978 to 3057 (aromatic CH triplet) 1605 (benzyl singlet). ^{1}H NMR ($CDCl_3$) 7.0 to 7.8 (m, phenyl), 3.9 (t, benzylic), 2.9 (t), 2,2 (s, broad –OH).

RESULTS AND DISCUSSION

The absence of bromine in our chemical store and its non-availability in our immediate environment necessitated its production from an intimate mixture of NaBr and MnO_2 in the presence of conc. H_2SO_4. The reaction in addition to producing Br_2, generated a considerable amount of HBr. This may be reflective of reduced mixture-intimacy. The generated Br_2 was reacted with dry benzene in the presence of pyridine to give bromobenzene. The reaction of benzene with Br_2 was initially quite vigorous with liberation of HBr which was absorbed by use of a gas trap. With bromobenzene in hand, the Grignard reaction was effected with magnesium ribbon, cut up into little bits, in dry diethyl ether. The phenylmagnesium bromide was then reacted with 1,2-dibromoethane (Scheme 2). It was previously prepared by the reaction of Br_2 and ethane, which was itself prepared by dehydration of ethanol.

In the preparation of 1,2-dibromoethane, ethene, which was liberated as a gas at 150 to 170°C was passed through a bottle trap, to which was connected a delivery tube that dipped into the bottom of a subsequent round-bottom flask containing bromine in water. The bromine in water was a heterogeneous mixture, with reddish-brown lower layer. As the ethene gas bubbled through the bromine, the flask became hot and with time, the bromine colour was discharged and in its place was a clear upper aqueous layer and a lower organic phase. Some diethyl ether was also formed as a side reaction.

Usually, in running a Grignard reaction, the Grignard reagent is first prepared in a flask while the alkyl halide is dripped into the Grignard. In this case, the alkyl halide has two electrophilic centres, which are equally susceptible to attack. The initial product is 2-phenylethyl bromide. However, given that in the normal Grignard reaction mode there is excess of Grignard reagent, the presence of an alkyl halide in the initial product renders it susceptible to further Grignard attack with consequent formation of 1,2-diphenylethane. This would destroy the bromide functionality which is required to be hydroxylated to the alcohol. To obviate this, a reverse Grignard mode was effected, in which the phenylmagnesium bromide was transferred to a dropping funnel protected with a drying tube, while 1,2-dibromoethane was in the reaction flask. In this way, there is an excess of the dibromide in the reaction medium, with concomitant likelihood of generating the desired 2-phenylethyl bromide which was then converted to 2-phenylethanol by alkaline hydroxylation. The 2-phenylethanol showed a broad –OH stretch at 3215 to 3400 cm^{-1}, a triplet aromatic peak at 2978 to 3057 and a benzyl stretch at 1605 cm^{-1}. Also, the ^{1}H NMR showed a phenyl group at 7.0 to 7.88 ppm, a triplet for benzylic protons at 3,9 ppm, a triplet at 2,9 ppm representing the two protons attached to the carbon bearing the hyrdoxyl group and a broad singlet for the hydroxyl proton.

Conclusion

The production of 2-phenylethanol by reaction of

phenyl-magnesium bromide with 1,2-dibromoethane, in a reverse Grignard mode gave 2-phenylbromoethane which was hydrolyzed with sodium hydroxide resulting in 2-phenylethanol.

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