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Investigation of the l-phenylacetylcarbinol process to substituted benzaldehydes of interest

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ABSTRACT

The large scale industrial manufacture of the nasal decongestant pseudoephedrine is typically carried out by the reductive amination of l-phenylacetylcarbinol (l-PAC), which in turn is produced via the biotransformation of benzaldehyde using yeast. In recent years there has been increasing legislative control of the supply of pseudoephedrine due to it being diverted for the clandestine production of methylamphetamine and there is some evidence that a number of clandestine drug laboratory chemists have considered the application of the l-PAC process to manufacture their own pseudoephedrine. This work examined the use of a number of substituted benzaldehydes for the manufacture of the corresponding substituted l-PAC analogue followed by reductive amination to the corresponding substituted pseudoephedrine/ephedrine analogues. These substituted pseudoephedrine/ephedrine analogues were either reduced or oxidised to determine the feasibility of producing the corresponding methylamphetamine or methcathinone analogues. As a result, the l-PAC process was identified as a viable route for synthesis of substituted methylamphetamines and methcathinones.

1. Introduction

The l-phenylacetylcarbinol (l-PAC) process is a biotransformation process using the fungus yeast. The mechanism, which was initially investigated by Neuberg et al. [1,2], involves glycolysis of glucose to produce pyruvic acid which is then decarboxylated by pyruvate decarboxylase to produce acetaldehyde. The resulting acetaldehyde then undergoes a condensation reaction with benzaldehyde to produce l-PAC [(*R*)-1-hydroxy-1-phenylpropan-2-one]. During this process, by-products are formed due to the action of alcohol dehydrogenase on benzaldehyde and l-PAC resulting in benzyl alcohol and (1*R*,2*S*)-1-phenylpropan-1,2-diol (PAC-diol) respectively.[3,4] (refer to Scheme 1).

The l-PAC process has previously been employed by the pharmaceutical industry due to the ease with which l-PAC can be chemically converted to pseudoephedrine/ephedrine. In recent years, a number of clandestine drug laboratories have been located which have exploited the commercial process for the production of pseudoephedrine/ephedrine for use in the manufacture of methylamphetamine [3].

Global controls over the supply of pseudoephedrine as a potential illicit drug precursor has heightened the possibility that this process will gain increased importance in illicit drug production. This process has dual applicability in that the pseudoephedrine/ephedrine produced by this process can be employed for both methylamphetamine and methcathinone production.

The work presented here aimed to investigate the l-PAC process as a viable manufacturing pathway to produce a variety of substituted methylamphetamines and methcathinones and hence identify the potential emerging precursor chemicals for substituted methylamphetamine and methcathinone analogues.

2. Materials and methods

2.1. Materials

Piperonal (3,4-methylenedioxybenzaldehyde), acetaldehyde, benzaldehyde, hypophosphorous acid, 50% (w/w), sodium bicarbonate, sodium carbonate, sodium chloride and trisodium citrate were purchased from Sigma–Aldrich. 4-(Methylthio)benzaldehyde, 4-fluorobenzaldehyde and sodium borohydride were purchased from Alfa Aesar. 4-Methylbenzaldehyde, 4-anisaldehyde (4-methoxybenzaldehyde), Celite 545 (particle size 0.02–0.1 mm) and analytical grade ethanol were purchased from Merck. Citric acid monohydrate, ethyl acetate, hydrochloric acid 32% and sodium hydroxide were purchased from Ajax Fine Chemicals.

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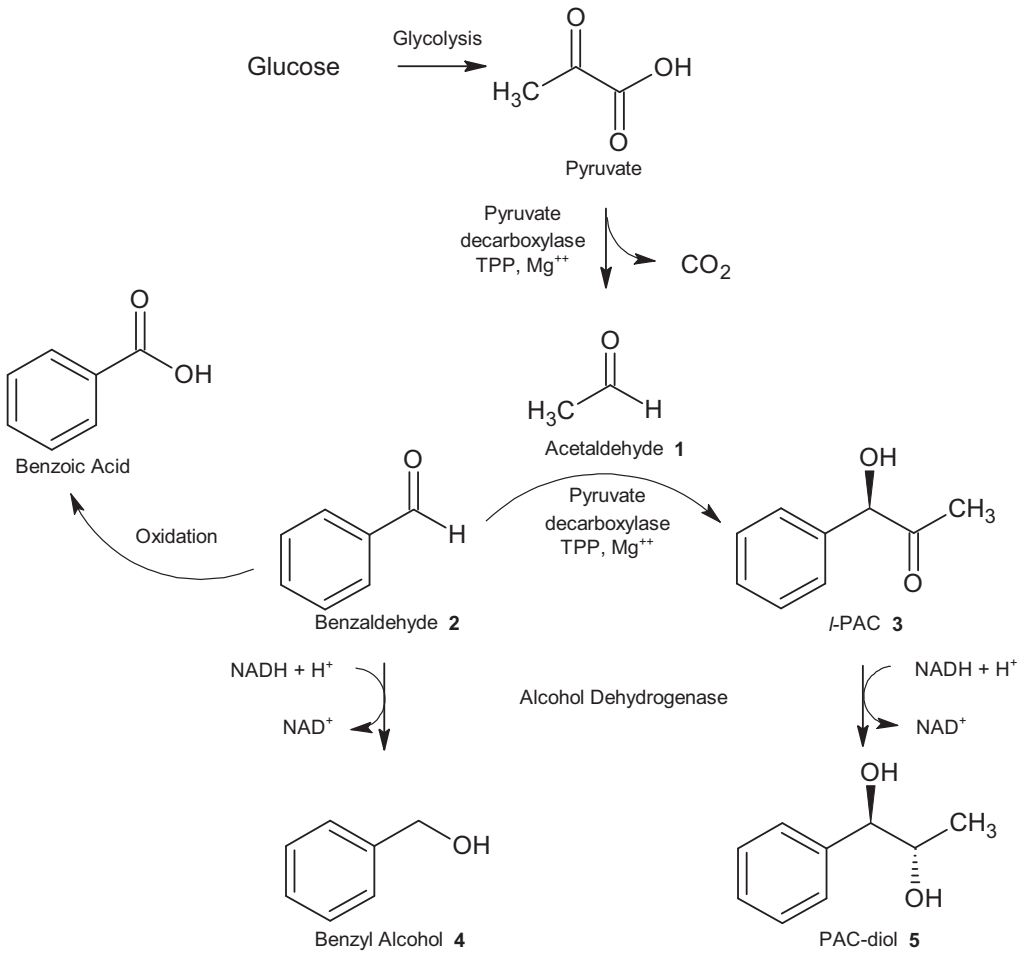

Scheme 1. Mechanism of the fermentation of benzaldehyde to produce l-PAC and various byproducts [3,4].

Chloroform, dichloromethane and diethyl ether were purchased from Macron Fine Chemicals, J.T.Baker and BioLab respectively. Iodine, methylamine aqueous solution 40%, sodium dichromate dihydrate and sulphuric acid were purchased from Asia Pacific Specialty Chemicals LTD, Prolabo, Fluka and BDH respectively. Sodium hydrosulfite and sodium sulphate anhydrous granular were purchased from Chem-Supply. All reagents and solvents purchased were of analytical grade and not further purified before use. Dextose (glucose), manufactured by Brigalow Natural Products and Instant Dried, Premium Bakers' Yeast (species *Saccharomyces cerevisiae*), manufactured by Lowan Whole Foods was purchased from a local supermarket.

2.2. Instrumentation

Gas chromatography–mass spectrometry (GC–MS) analyses were performed on an Agilent HP-6890N Network GC system using an Agilent HP-5MS capillary column (30 m × 0.25 μm) fitted with an Agilent HP-5973 mass selective detector. The carrier gas was helium at a constant flow of 1.0 mL/min and a split ratio of 25:1 with an injection volume of 0.2 μL The injector temperature was set to 100 °C, with an initial oven temperature of 100 °C held for 1 min, then ramped at 30 °C/min to 280 °C and held there for 10 min. The mass selective detector operated between $m/z = 40$ and 450 in electron impact mode with an ionisation energy of 70 eV.

Gas chromatography-vapour phase infrared (GC-IRD) analyses were performed on an Agilent HP-7890A GC system using an Agilent HP-5MS capillary column (30 m × 0.25 μm) fitted with an ASAP IRD II infrared detector. The carrier gas was helium at a constant flow of 4.2 mL/min. The injector was set at a pulsed split of 24 psi for 2 min with a split ratio of 1:1 and an injection volume of 2 μL The injector temperature was set to 100 °C, with an initial oven temperature of 100 °C held for 2 min, then ramped at 20 °C/min to 280 °C and held there for 8 min. The temperature of the transfer lines and light pipe were kept at 250 °C and the IRD II's scanning range was set to 4000–500 cm^{-1}.

Nuclear magnetic resonance (NMR) analysis was carried out using a Varian 400 MHz Unity INOVA spectrometer operating at 400 MHz (^1H) and 100 MHz (^{13}C). Samples were run in a mixed solvent system of d^6DMSO and $CDCl_3$ at 298 K. ^1H spectra were referenced to the d^6DMSO solvent residual taken as 2.49 ppm and ^{13}C spectra were referenced to the d^6DMSO solvent residual taken at 39.50 ppm at the temperature quoted.

2.3. General fermentation procedure

Yeast (44 g) and glucose (310 mmol) were added to a beaker and placed in a water bath heated to 30 °C. To this, 500 mL of a 0.1 M citrate buffer (pH 5) consisting of 7.35 g trisodium citrate and 5.25 g citric acid in deionised water was added. The broth was stirred for 40 min before a substituted benzaldehyde (25 mmol) in 5 mL ethanol and acetaldehyde (30 mmol) was added to the broth. After being left to ferment for approximately 60 min, the broth was filtered through Celite and extracted with ethyl acetate (3× 100 mL). Emulsions in the extract were broken through the use of a saturated sodium chloride solution, dried over anhydrous sodium sulphate, filtered and evaporated. The crude reaction product was