



The synthesis and characterisation of MDMA derived from a catalytic oxidation of material isolated from black pepper reveals potential route specific impurities



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ABSTRACT

This work examines the chemical synthesis of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) from piperonal prepared via a catalytic ruthenium tetroxide oxidation of piperine extracted from black pepper. A variety of oxidation conditions were experimented with including different solvent systems and co-oxidants. A sample of prepared piperonal was successfully converted into MDMA via 3,4-methylenedioxyphenyl-2-nitropropene (MDP2NP) and 3,4-methylenedioxyphenyl-2-propanone (MDP2P) and the impurities within each product characterised by GC-MS to give a contaminant profile of the synthetic pathway. Interestingly, it was discovered that a chlorinated analogue of piperonal (6-chloropiperonal) was created during the oxidation process by an as yet unknown mechanism. This impurity reacted alongside piperonal to give chlorinated analogues of each precursor, ultimately yielding 2-chloro-4,5-methylenedioxyamphetamine (6-Cl-MDMA) as an impurity within the MDMA sample. The methodology developed is a simple way to synthesise a substantial amount of precursor material with easy to obtain reagents. The results also show that chlorinated MDMA analogues, previously thought to be deliberately included adulterants, may in fact be route specific impurities with potential application in determining the origin and synthesis method of seized illicit drugs.

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1. Introduction

MDMA (3,4-methylenedioxy-*N*-methylamphetamine) is a synthetic amphetamine derivative that has both stimulant and hallucinogenic properties [1]. Although first patented by Merck in 1912 as a precursor to a new pharmaceutical, the pharmacological effects were not studied until fifteen years later whilst the recreational use of MDMA remained relatively unknown until the early 1980's [2]. The 2012–2013 Australian Crime Commission illicit drug data report showed that MDMA was the third most widely used drug in Australia, after cannabis and methamphetamine [3], whilst a national survey conducted in 2007 stated that 8.9% of the population (1.5 million people) reported lifetime use of the drug [4].

Like the parent compounds, amphetamine and methamphetamine, MDMA is a powerful central nervous system (CNS) stimulant, although its mechanism of action is fundamentally different. Whilst the effects of the amphetamines are mediated by dopamine and noradrenaline, MDMA primarily acts on the serotonergic system [5]. MDMA has a high affinity for the serotonin transporter and acts by reversing its normal reuptake action, releasing up to 80% of available serotonin into the synaptic cleft [6]. Whilst there is still debate and research into the

topic, it is generally accepted that MDMA can act as a neurotoxin in humans [5,7].

MDMA is more commonly known by the street name 'ecstasy', and has recently made a resurgence on Australian soil after many years of near absence in seized specimens obtained by law enforcement [3]. It is typically found as the hydrochloride salt of the racemic mixture, often pressed into pill form and containing various adulterants such as caffeine or even other amphetamines. [8] The illegal clandestine manufacture of MDMA is most commonly performed via a reductive amination of 3,4-methylenedioxyphenyl-2-propanone (MDP2P) [9]. Most synthetic routes leading to this precursor begin with materials that already contain a pre-installed methylenedioxyphenyl moiety such as safrole, isosafrole and piperonal [10].

The chemical profiling of illegally synthesised drugs based on their impurities can assist in providing useful information for law enforcement agencies regarding the synthetic methodology employed and the precursor compound used, as well as information linking drug seizures and lab discoveries. Impurities are often identified using gas chromatography–mass spectrometry (GC-MS), although a more in depth analysis can be achieved on individual components using nuclear magnetic resonance (NMR) or Fourier transform infrared spectroscopy (FT-IR) [11–13]. The majority of studies involving the impurity profiling of MDMA have concentrated on the final synthetic steps, with little attention paid to the origin of the precursor material [11].

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The precursor compound piperonal could theoretically be synthesised in a clandestine setting by the oxidation of piperine, the major alkaloid present in black pepper. Piperonal could also be obtained via an oxidation reaction of piperic acid, which can be readily produced by the hydrolysis of piperine. There are multiple previous syntheses of piperonal from piperine and piperic acid, many located online on clandestine internet forums and written rather inaccurately. Only one study (Gallagher *et al.*) describes scientifically how piperonal could be successfully synthesised from both piperine and from the commercially available flavourant vanillin [11]. The authors successfully oxidised piperine via two different methodologies; an ozonation and a potassium permanganate oxidation. In our laboratory, permanganate oxidations have proven to be somewhat irreproducible, producing mixed quantities of the starting material and target compound, as well as the over-oxidised carboxylic acid analogue. An ozonolysis, arguably the most feasible and clean methodology for such an oxidation, would be difficult to upscale in a clandestine setting but is possible on the small scale. Here we report the successful synthesis of MDMA from piperine extracted from black pepper by a catalytic oxidation using ruthenium chloride and a co-oxidant, which are both easily purchased online. Additionally, a variety of oxidation conditions are reported for the oxidation of piperine/piperic acid to the precursor compound piperonal. It was found that the oxidant that gave the best results, as well as being the most readily available, was the commercially available pool oxidant Oxone® (potassium peroxy sulfate). Our results show that chlorinated MDMA analogues, previously thought to be deliberately included adulterants, may in fact be route specific impurities of potential diagnostic value to law enforcement. These chlorinated analogues can also be considered valuable trace impurities for the identification of which synthetic route was used to produce clandestinely synthesised MDMA.

2. Methods

2.1. Rationale

We envisioned a new, upscalable methodology that would use commercially available starting materials and that could afford a high quality piperonal precursor. The catalytic oxidant that was settled upon was ruthenium tetroxide (RuO_4), which can be prepared *in situ* by the action of an oxidant on ruthenium chloride (RuCl_3). The inexpense and availability of ruthenium chloride, which is easily available via the internet, make this route potentially attractive for the clandestine synthesis of piperonal. On a larger scale, the ability to recover and reuse spent ruthenium catalyst also makes this an attractive reaction for clandestine synthesis. The oxidation can be conveniently carried out in a biphasic system using a chlorinated solvent, and requires a catalytic amount of RuCl_3 alongside an oxidant such as NaIO_4 , HIO_4 , NaOCl or NaBrO_3 [14]. The addition of acetonitrile leads to a greatly improved oxidation system due to its ability to return deactivated ruthenium carboxylate complexes back into the catalytic cycle [15]. The catalytic cycle begins within the aqueous phase when RuCl_3 reacts with the oxidant to become the solvent soluble species RuO_4 . The RuO_4 migrates into the non-polar phase, oxidises an organic molecule solubilised within, then returns to the aqueous phase thereby completing the catalytic cycle (Fig. 1).

2.2. Equipment and reagents

Unless otherwise noted, all materials were synthesis grade and obtained from Sigma-Aldrich (Castle Hill, NSW, Australia) and were used as received. Ruthenium chloride and GLB® Oxy-Bright® (containing 41.3% DuPont Oxone® by weight) were purchased from eBay. Thin-layer chromatography was carried out on aluminium-backed SiO_2 gel TLC plates (60 F₂₅₄), which were visualised with UV light (254 nm). Flash column chromatography was carried out with

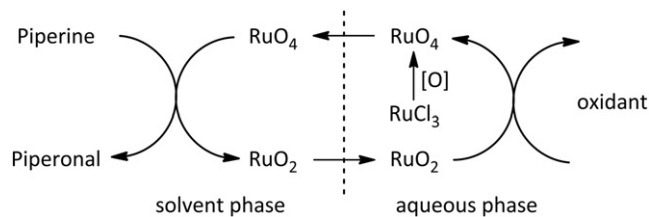


Fig. 1. Catalytic cycle of the ruthenium oxidation.

Davisil LC35a SiO_2 (40–63 μm). NMR spectra were obtained with a Bruker Avance III 300 MHz spectrometer where the residual solvent peaks from the deuterated solvents (CDCl_3 : ^1H δ = 7.27 ppm, ^{13}C δ = 77.0 ppm; $[\text{D}_6]$ DMSO: ^1H δ = 2.5 ppm, ^{13}C δ = 128 ppm) were used as reference. ^1H NMR was obtained with a minimum of 16 scans, ^{13}C NMR was obtained with a minimum of 1024 scans. GC-MS analysis was performed on an Agilent 5973 MSD gas chromatograph. Analytes were separated using an Agilent DB-5 ms column, 30.0 m long, with an internal diameter of 250 μm , 0.25 μm film. Helium was used as the carrier gas at 1.5 mL/min. The injection volume was 1 μL made splitless by the autosampler. The following temperature program was used; 60 °C maintained for 1 min, then ramped to 325 °C at 10 °C/min. Mass spectrometry was performed in electron ionisation mode and a full mass spectrum from 50 to 400 amu was obtained. Database matches were made using the NIST-11 mass spectral library.

2.3. Extraction of piperine from pepper [16]

A 1200 mL aliquot of ethanol was added to ground black pepper (200 g) and the resulting suspension was refluxed for 2 h. The insoluble material was separated by vacuum filtration and the filtrate concentrated under reduced pressure. The residual oil was then taken up in a 10% KOH in ethanol solution (150 mL), triturated with H_2O until the point of permanent turbidity and then left at 4 °C overnight. The solution was then filtered and the residual solid recrystallised from acetone/hexane to give piperine (9.72 g, 4.86%) as an orange solid. An analogous extraction using white pepper (200 g) provided piperine (7 g, 3.5%) as an orange solid. ^1H NMR: see Fig. S1. ^{13}C NMR: see Fig. S2. ^1H NMR (300 MHz, CDCl_3): δ 7.46–7.37 (m, 1H), 6.99 (d, J = 1.7 Hz, 1H), 6.90 (dd, J = 8.1, 1.7 Hz, 1H), 6.81–6.68 (m, 3H), 6.45 (d, J = 14.7 Hz, 1H), 5.99 (s, 2H), 3.69–3.50 (m, 4H), 1.72–1.55 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 165.2, 148.0, 147.9, 142.3, 138.0, 130.8, 125.2, 122.3, 119.9, 108.3, 105.5, 101.1, 46.7, 43.1, 26.6, 25.5, 24.5.

2.4. Hydrolysis of piperine to piperic acid [17]

Piperine (3.53 g, 12.37 mmol) was dissolved in a 10% KOH in ethanol solution (50 mL) and refluxed for 24 h. After 24 h, H_2O (100 mL) was added and the solution was washed with ethyl acetate (3×100 mL). The aqueous phase was acidified to pH 1 with conc. HCl and subsequently extracted using ethyl acetate (3×100 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure to yield yellow crystals of piperic acid (1.89 g, 70.3%). ^1H NMR: see Fig. S3. ^{13}C NMR: see Fig. S4. ^1H NMR (300 MHz,

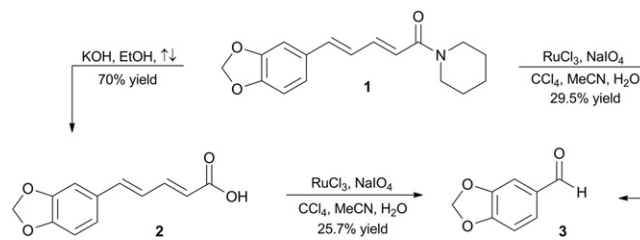


Fig. 2. Synthetic pathway from piperine (1) and piperic acid (2) to piperonal (3).

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