



# 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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## ARTICLE INFO

### Article history:

Received 22 October 2015

Received in revised form 27 January 2016

Accepted 29 January 2016

### Keywords:

MDMA

Clandestine synthesis

Pepper

Ruthenium tetroxide

Route specific impurities

## 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 ( $\text{RuO}_4$ ), which can be prepared *in situ* by the action of an oxidant on ruthenium chloride ( $\text{RuCl}_3$ ). 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  $\text{RuCl}_3$  alongside an oxidant such as  $\text{NaIO}_4$ ,  $\text{HIO}_4$ ,  $\text{NaOCl}$  or  $\text{NaBrO}_3$  [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  $\text{RuCl}_3$  reacts with the oxidant to become the solvent soluble species  $\text{RuO}_4$ . The  $\text{RuO}_4$  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  $\text{SiO}_2$  gel TLC plates (60 F<sub>254</sub>), which were visualised with UV light (254 nm). Flash column chromatography was carried out with

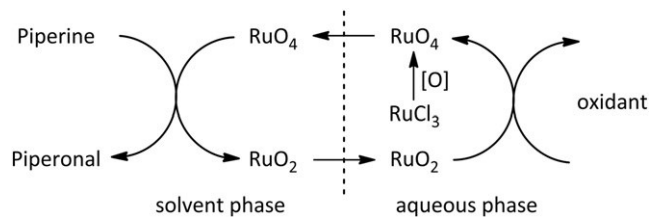


Fig. 1. Catalytic cycle of the ruthenium oxidation.

Davisil LC35a  $\text{SiO}_2$  (40–63  $\mu\text{m}$ ). NMR spectra were obtained with a Bruker Avance III 300 MHz spectrometer where the residual solvent peaks from the deuterated solvents ( $\text{CDCl}_3$ :  $^1\text{H}$   $\delta$  = 7.27 ppm,  $^{13}\text{C}$   $\delta$  = 77.0 ppm;  $[\text{D}_6]$ DMSO:  $^1\text{H}$   $\delta$  = 2.5 ppm,  $^{13}\text{C}$   $\delta$  = 128 ppm) were used as reference.  $^1\text{H}$  NMR was obtained with a minimum of 16 scans,  $^{13}\text{C}$  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  $\mu\text{m}$ , 0.25  $\mu\text{m}$  film. Helium was used as the carrier gas at 1.5 mL/min. The injection volume was 1  $\mu\text{L}$  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  $\text{H}_2\text{O}$  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.  $^1\text{H}$  NMR: see Fig. S1.  $^{13}\text{C}$  NMR: see Fig. S2.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{H}_2\text{O}$  (100 mL) was added and the solution was washed with ethyl acetate ( $3 \times 100$  mL). The aqueous phase was acidified to pH 1 with conc. HCl and subsequently extracted using ethyl acetate ( $3 \times 100$  mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to yield yellow crystals of piperic acid (1.89 g, 70.3%).  $^1\text{H}$  NMR: see Fig. S3.  $^{13}\text{C}$  NMR: see Fig. S4.  $^1\text{H}$  NMR (300 MHz,

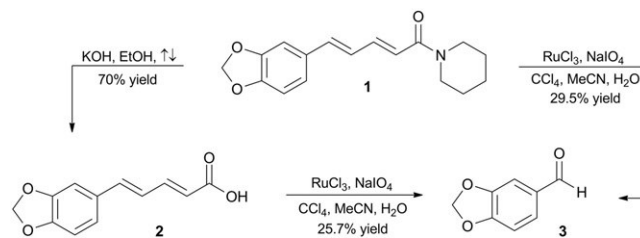
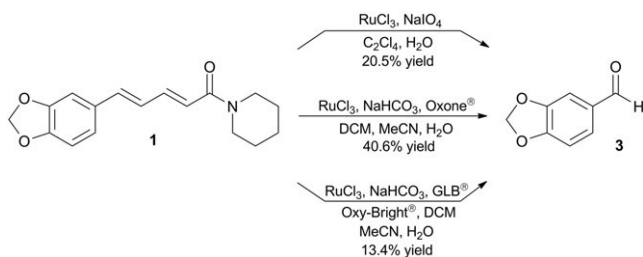


Fig. 2. Synthetic pathway from piperine (1) and piperic acid (2) to piperonal (3).



**Fig. 3.** Various oxidation conditions trialed in the synthesis of piperonal (3) from piperine (1).

[D<sub>6</sub>]DMSO):  $\delta$  12.23 (s, 1H), 7.34–7.23 (m, 2H), 7.04–6.90 (m, 4H), 6.05 (s, 2H), 5.92 (d,  $J$  = 15.1 Hz, 1H). <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta$  167.6, 148.1, 148.0, 144.6, 139.7, 130.5, 124.8, 123.1, 121.1, 108.5, 105.7, 101.3.

### 2.5. Trial scale oxidative cleavage of piperine to piperonal

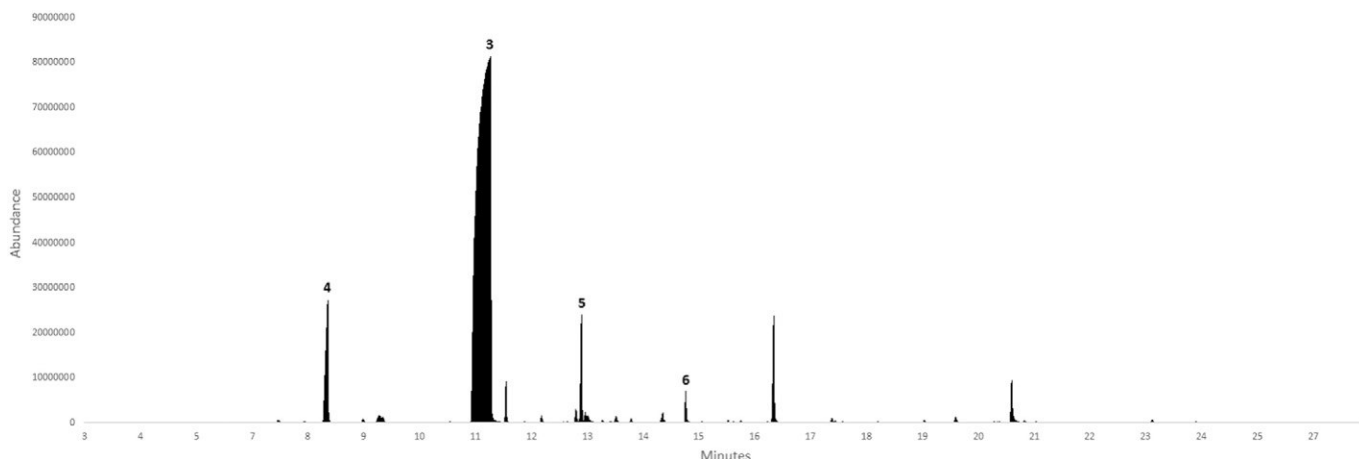
Piperine (514 mg, 1.8 mmol) was dissolved in the solvent mixture [see below] before  $\text{RuCl}_3$  (75 mg, 0.36 mmol, 0.2 equiv) and the oxidant [see below] were added. The mixture was stirred for 24 h, then further  $\text{RuCl}_3$  (75 mg, 0.36 mmol, 0.2 equiv) and oxidant were added. The solution was stirred for a further 24 h. The reaction mixture was then poured into  $\text{H}_2\text{O}$  (100 mL), and the resulting mixture was extracted with dichloromethane ( $3 \times 100$  mL). The combined organic extracts were washed with a saturated solution of sodium thiosulfate (100 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (1:9 – ethyl acetate/hexane) to give an accurate yield of piperonal as described below.

**System 1:** Solvent =  $\text{H}_2\text{O}$  (25 mL), acetonitrile (25 mL), and  $\text{CCl}_4$  (10 mL). Oxidant =  $\text{NaIO}_4$  (770 mg, 3.6 mmol, 2 equiv). Isolated yield = 29.5%.

**System 2:** Solvent =  $\text{H}_2\text{O}$  (20 mL) and  $\text{C}_2\text{Cl}_4$  (15 mL). Oxidant =  $\text{NaIO}_4$  (770 mg, 3.6 mmol, 2 equiv). Isolated yield = 20.5%.

**System 3:** Solvent =  $\text{H}_2\text{O}$  (20 mL), acetonitrile (20 mL) and dichloromethane (10 mL). Oxidant = Oxone<sup>®</sup> (2.22 g, 3.6 mmol, 2 equiv., calc. for  $\text{KHSO}_5$ ) and  $\text{NaHCO}_3$  (760 mg, 9 mmol, 5 equiv). Isolated yield = 40.6%.

**System 4:** Solvent =  $\text{H}_2\text{O}$  (20 mL), acetonitrile (20 mL), and dichloromethane (10 mL). Oxidant = GLB<sup>®</sup> Oxy bright<sup>®</sup> (41.3% Oxone<sup>®</sup> by weight) (5.38 g, 3.6 mmol, 2 equiv., calc. For  $\text{KHSO}_5$ ) and  $\text{NaHCO}_3$  (760 mg, 9 mmol, 5 equiv). Isolated yield = 13.4%.



**Fig. 4.** Gas chromatogram of the piperine (1) to piperonal (3) oxidation reaction.

### 2.6. Oxidative cleavage of piperic acid to piperonal

This was carried out as per 'system 1' (above) but using piperic acid (393 mg, 1.8 mmol) in place of piperine. Isolated yield = 25.7%.

### 2.7. Large scale oxidative cleavage of piperine to piperonal using Oxone<sup>®</sup>

Piperine (8.5 g, 29.8 mmol) was dissolved in acetonitrile (300 mL),  $\text{H}_2\text{O}$  (300 mL) and dichloromethane (150 mL) and sodium bicarbonate (12.5 g), ruthenium chloride (1.2 g) and Oxone<sup>®</sup> (36.5 g) were added. The mixture was stirred for 24 h before a further amount of sodium bicarbonate (12.5 g), ruthenium chloride (1.2 g) and Oxone<sup>®</sup> (36.5 g) were added. The solution was stirred for another 24 h before being poured into  $\text{H}_2\text{O}$  (300 mL) and extracted with dichloromethane ( $3 \times 200$  mL). The combined organic extracts were washed with a saturated solution of sodium thiosulfate (200 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residual oil was then vacuum distilled using a Kugelrohr apparatus to give piperonal (1.51 g, 33.7%) as a yellow solid. <sup>1</sup>H NMR: see Fig. S5. <sup>13</sup>C NMR: see Fig. S6. GC-MS: see Fig. 4. <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.78 (s, 1H), 7.38 (dd,  $J$  = 7.93, 1.70 Hz, 1H), 7.30 (d,  $J$  = 1.51 Hz, 1H), 6.90 (d,  $J$  = 7.93 Hz, 1H), 6.05 (s, 2H). <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  190.2, 153.0, 148.6, 131.7, 128.6, 108.2, 106.7, 102.1.

### 2.8. Synthesis of 3,4-methylenedioxyphenyl-2-nitropropene (MDP2NP) (7) from piperonal [18]

To a solution of piperonal (1 g, 6.7 mmol) in acetic acid (5 mL) was added nitroethane (1 mL) followed by cyclohexylamine (0.7 mL) and the mixture was held at 100 °C for 6 h. The mixture was then diluted with  $\text{H}_2\text{O}$  (1 mL) and left at 4 °C overnight before being filtered to yield 3,4-methylenedioxyphenyl-2-nitropropene (0.75 g, 55%) as yellow crystals. <sup>1</sup>H NMR: see Fig. S7. <sup>13</sup>C NMR: see Fig. S8. GC-MS: see Fig. S13. <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03 (s, 1H), 7.02–6.88 (m, 3H), 6.06 (s, 2H), 2.47 (d,  $J$  = 0.97 Hz, 3H). <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.2, 148.1, 146.0, 133.5, 126.1, 125.9, 109.4, 108.7, 101.7, 14.0.

### 2.9. 3,4-Methylenedioxyphenyl-2-propanone (MDP2P) from MDP2NP [18]

To a refluxing suspension of iron dust (1.5 g) in acetic acid (6.5 mL) was added dropwise a solution of 3,4-methylenedioxyphenyl-2-nitropropene (0.45 g, 2.17 mmol) in acetic acid (4 mL). The resulting mixture was stirred at reflux for 2 h before being diluted with  $\text{H}_2\text{O}$  and extracted with dichloromethane ( $3 \times 50$  mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced

**Table 1**  
Tabulated impurities of the piperine (1) to piperonal (3) oxidation reaction.

	Molecular structure	Name	NIST match
4		1-piperidinecarboxaldehyde	91%
5		6-chloropiperonal	96%
6		2-propenal, 3-(1,3-benzodioxol-5-yl)	70%

pressure to yield 3,4-methylenedioxyphenyl-2-propanone (0.4 g, quant.) as a brown oil.  $^1\text{H}$  NMR: see Fig. S9.  $^{13}\text{C}$  NMR: see Fig. S10. GC-MS: see Fig. S14.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.78 (d,  $J = 7.74$  Hz, 1H), 6.69–6.62 (m, 2H), 5.95 (s, 2H), 3.61 (s, 2H), 2.15 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.3, 147.5, 146.3, 127.5, 122.1, 109.4, 108.0, 100.7, 50.0, 28.7.

#### 2.10. 3,4-Methylenedioxy-methamphetamine (MDMA) from MDP2P [12,18]

An aluminium and mercury amalgam was prepared by the addition of mercuric chloride (6 mg) to freshly-cut aluminium foil (250 mg) in  $\text{H}_2\text{O}$  (18 mL). Once amalgamation was complete the  $\text{H}_2\text{O}$  was decanted and the aluminium was washed with  $\text{H}_2\text{O}$  ( $2 \times 30$  mL). To the aluminium amalgam was sequentially added methylamine hydrochloride (375 mg) in  $\text{H}_2\text{O}$  (375  $\mu\text{L}$ ), isopropanol (1.1 mL), 25% aqueous sodium hydroxide (880  $\mu\text{L}$ ) and 3,4-methylenedioxyphenyl-2-propanone (330 mg, 1.85 mmol) in isopropanol (2.2 mL). The reaction was kept below  $50^\circ\text{C}$  and stirred overnight before being extracted with dichloromethane ( $3 \times 50$  mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to yield 3,4-methylenedioxy-methamphetamine (300 mg, 84%) as a yellow oil.  $^1\text{H}$  NMR: see Fig. S11.  $^{13}\text{C}$  NMR: see Fig. S12. GC-MS: see Fig. 6.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.57–6.42 (m, 3H), 5.71 (s, 2H), 2.60–2.31 (m, 3H), 2.22 (s, 3H), 1.30 (bs, 1H), 0.87 (dd,  $J = 6.04$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.0, 145.3, 132.6, 121.5, 108.9, 107.5, 100.2, 55.8, 42.5, 33.4, 19.0.

### 3. Results and discussion

We began by extracting piperine from pepper using ethanol as an extraction solvent. [16] A 10% KOH in ethanol dissolution of the residual oil was successful in the precipitation of relatively pure crystals of piperine in a 4.9% yield and 3.5% yield from pre-ground black and white pepper, respectively. The first oxidation system that was

experimented with was a carbon tetrachloride ( $\text{CCl}_4$ ), acetonitrile (MeCN) and sodium metaperiodate ( $\text{NaIO}_4$ ) system as these conditions are abundant within the literature. Many methodologies called for two additions of both the ruthenium catalyst and the oxidant spaced up to a day apart, presumably due to catalyst deactivation. Piperine has two carbon–carbon alkene bonds that can potentially be oxidised so in theory a total of two equivalents of oxidant would be all that would be required. When such reactions were trialled it was found that a quantifiable amount of starting material was continuously present.

It was discovered that a total of four equivalents of oxidant, that is separate additions of two equivalents spaced a day apart, afforded somewhat pure piperonal, which after chromatographic isolation gave pure piperonal in an acceptable oxidation yield of 29.5% (Fig. 2). In an attempt to compare yields and also discover if it would be possible to obtain a purer crude product, experiments with the oxidation of piperic acid in place of the usual piperine were trialled. Piperic acid was prepared by the hydrolysis of piperine in a 10% potassium hydroxide in ethanol reflux, yielding piperic acid in a 70% yield as fine yellow crystals [17]. The ruthenium oxidation reaction of piperic acid was found to give a purer piperonal product that did not contain the same level of aliphatic impurities upfield in the  $^1\text{H}$  NMR, as was expected. Due to the mostly similar yield and purity it was decided that piperine was the better candidate for the clandestine oxidation to produce piperonal.

Once successful oxidation conditions had been discovered attempts were made towards making the reaction more clandestinely viable. One such attempt involved a switch from the  $\text{CCl}_4/\text{MeCN}$  solvent system to a pure tetrachloroethylene ( $\text{C}_2\text{Cl}_4$ ) solvent system, as tetrachloroethylene is commercially available in a relatively pure form for use as dry cleaning fluid. This reaction was found to be successful, albeit only providing piperonal (3) in a 20.5% yield as opposed to the 29.5% yield discovered for the dual solvent system. The fact that the acetonitrile had been omitted could be visibly appreciated by the precipitation of inactivated catalyst on the sides of the reaction vessel. A switch from sodium metaperiodate to the commercially available swimming pool oxidant Oxone<sup>®</sup> was then experimented with.

Oxone<sup>®</sup> exists as the stable triple salt  $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ , with the active component potassium peroxomonosulfate ( $\text{KHSO}_5$ ) only making up about 50% of the total mixture [19]. Oxone<sup>®</sup> is readily available in kilogram quantities and is a cheap industrial chemical. Previous research into similar ruthenium oxidation systems found that the addition of sodium bicarbonate ( $\text{NaHCO}_3$ ) was required to buffer the reaction system [20]. A chlorinated solvent change from carbon tetrachloride to dichloromethane (DCM) was also made to better imitate clandestine reaction settings. Reactions using reagent grade Oxone<sup>®</sup> provided piperonal (3) in a 40.6% yield, a much better yield than the analogous reaction using sodium metaperiodate which only

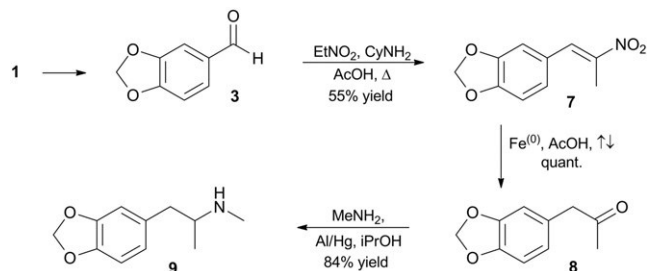
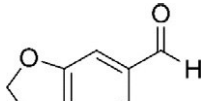
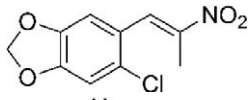
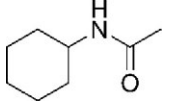
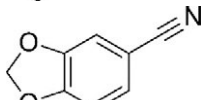
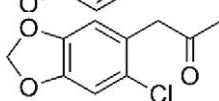
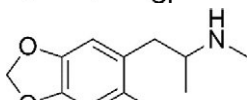
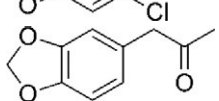
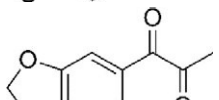
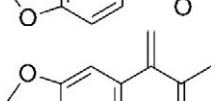
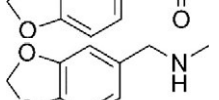
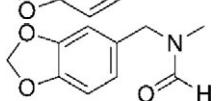
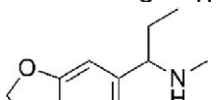
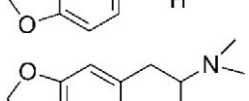
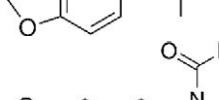
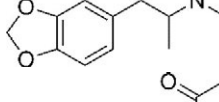
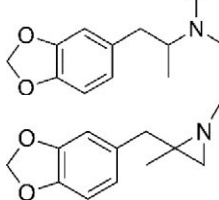


Fig. 5. Nitropropene synthetic pathway to MDMA (9) from piperine (1).

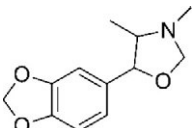
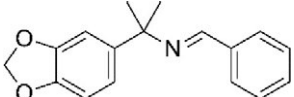
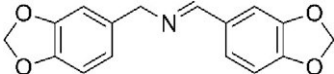
Table 2

Tabulated impurities encountered during MDMA synthesis via the nitropropene and reductive amination synthetic methodologies.

Molecular structure	Name	Detected in	NIST match
	Piperonal	MDP2NP, MDP2P, MDMA	96%
	2-chloro-4,5-methylenedioxyphenyl-2-nitropropene (6-Cl-MDP2NP)	MDP2NP	99%
	<i>N</i> -cyclohexylacetamide	MDP2NP, MDP2P, MDMA	95%
	Piperonylonitrile	MDP2NP, MDP2P	91%
	2-chloro-4,5-methylenedioxyphenyl-2-propanone (6-Cl-MDP2P)	MDP2P, MDMA	96%
	2-chloro-4,5-methylenedioxymethamphetamine (6-Cl-MDMA)	MDMA	78%
	3,4-methylenedioxyphenyl-2-propanone (MDP2P)	MDMA	91%
	1,2-propanedione,1-(3,4-methylenedioxy)phenyl	MDMA	86%
	3-[3,4-methylenedioxyphenyl]-3-buten-2-one	MDMA	96%
	3,4-methylenedioxy- <i>N</i> -methylbenzylamine	MDMA	90%
	<i>N</i> -formyl- <i>N</i> -methyl-3,4-methylenedioxybenzylamine	MDMA	93%
	1-methylamino-1-(3,4-methylenedioxyphenyl)propane	MDMA	83%
	<i>N,N</i> -dimethyl-3,4-methylenedioxyamphetamine	MDMA	87%
	<i>N</i> -formyl- <i>N</i> -methyl-3,4-methylenedioxyamphetamine	MDMA	70%
	<i>N</i> -acetyl-3,4-methylenedioxymethamphetamine	MDMA	91%
	1-((1,2-dimethyl-1-azacycloprop-2-yl)methyl)-3,4-methylenedioxybenzene	MDMA	81%

(continued on next page)

Table 2 (continued)

	Molecular structure	Name	Detected in	NIST match
24		3,4-dimethyl-5-(3,4-methylenedioxy)phenyloxazolidine	MDMA	90%
25		N-(3,4-methylenedioxyphenylisopropyl)benzaldimine	MDMA	94%
26		N-[(3,4-methylenedioxy)phenylmethyl]-3,4-(methylenedioxy)benzaldimine	MDMA	96%

provided piperonal (3) in a 29.5% yield. Owing to this success a commercially available pool oxidant formulation by GLB® pool care named Oxy-Bright® was experimented with. This formulation is 41.3% Oxone® with the rest made up of inert materials. Reactions ran indicated that this mixture was unsuitable and that one of the inert materials was poisoning the catalytic cycle, as yields were much lower at 13.4% (Fig. 3).

Large scale oxidation reactions of piperine (1) to piperonal (3) were attempted using analogous conditions developed for the small scale Oxone® oxidation. This reaction yielded a crude product which was purified via bulb–bulb distillation to provide a relatively pure piperonal sample as a yellow solid in a 33.7% yield and 86.6% purity (by GC-MS). The gas chromatograph and tabulated impurities of the product are presented in Fig. 4 and Table 1. Apart from piperonal (3), only three organic compounds could be identified. The impurities include cleaved fragments of the piperine molecule including 1-piperidinecarboxaldehyde (4) and the extended aldehyde, 2-propenal, 3-(1,3-benzodioxol-5-yl) (6). An interesting impurity to arise was 6-chloropiperonal, which was a 96% match to the corresponding spectra in the NIST database and was presumably chlorinated by an unknown mechanism involving the use of ruthenium chloride or dichloromethane during the oxidation reaction.

A sample of the piperonal synthesised from piperine was then converted to MDMA via the commonly encountered nitropropene and reductive amination synthetic pathway [12,18]. The first step involved a nitroaldol addition (Henry reaction) of the prepared piperonal (3) with nitroethane (EtNO<sub>2</sub>) in glacial acetic acid (AcOH) using cyclohexylamine (CyNH<sub>2</sub>) as a base. This provided the corresponding nitroalkene compound MDP2NP (7), generated by a condensation reaction between the aldehyde and nitroalkane precursor, as yellow

crystals in a 55% yield and 90.8% purity. The prepared MDP2NP was then reduced using iron filings in a glacial acetic acid reflux to give ketone MDP2P (8) as a brown oil in a quantitative yield and 91.3% purity. Reductive amination with methylamine using an aluminium and mercury amalgam provided the target amine MDMA (9) as a yellow oil in an 84% yield and 77.3% purity (Fig. 5).

Special care was taken during each of the synthetic steps to select conditions and reagents that could be present in a standard, albeit well equipped, clandestine laboratory setting. Purification between synthetic steps was limited to liquid–liquid extractions and precipitations, where applicable. GC-MS experiments were conducted on the crude product of each step along the synthetic route to MDMA to identify any impurities present (Table 2).

Many unexpected and unusual reaction products were identified within the prepared MDMA sample, as well as many common impurities (Fig. 6). Some of the common impurities included *N*-formylated (21), dimethylated (20) and acetylated (22) MDMA analogues, as well as a variety of benzylamine analogues (17–19). A compound containing a three-membered aziridine ring system (23) was an uncommon impurity that has previously been reported by Palhol *et al.* [21]. Another compound containing an oxazolidine ring system (24) was an unusual find, but had also been previously reported as an impurity during MDMA synthesis [22]. The presence of the impurity *N*-cyclohexylacetamide (11) indicates that cyclohexylamine was used as the base during the nitroaldol addition reaction. The other commonly used base for this reaction, ammonium acetate, cannot give rise to such an impurity.

To the best of our knowledge this is the first time that the unusual compounds 25 and 26 have been detected as a by-product to an MDMA synthesis. The compounds have a 94% and 96% library match

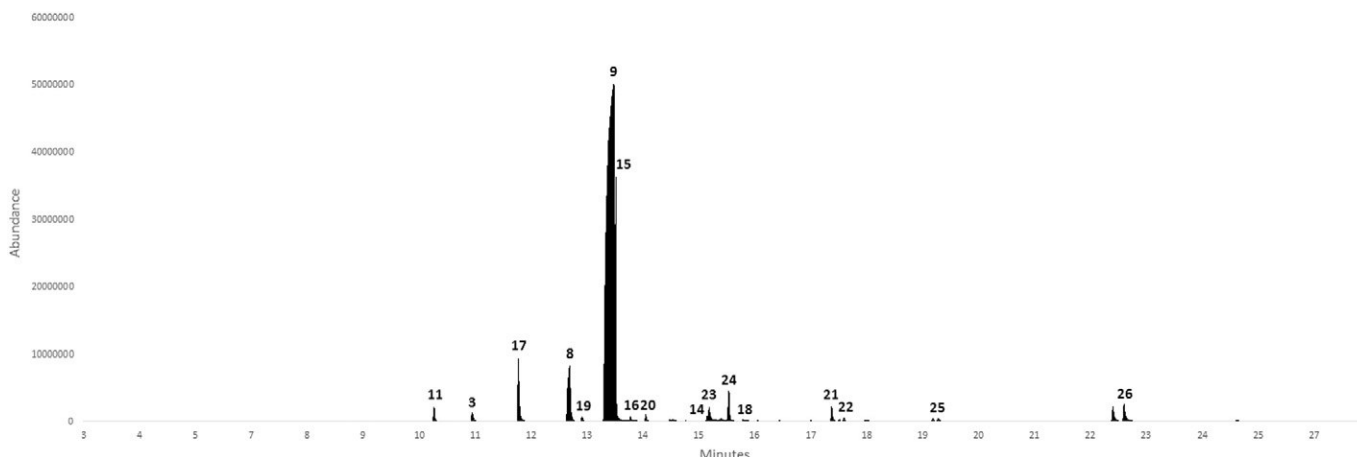
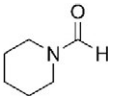
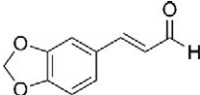
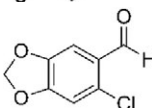
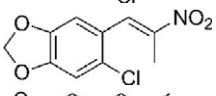
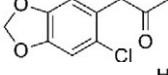
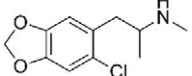


Fig. 6. Gas chromatogram of the prepared MDMA showing impurities.

**Table 3**  
Route specific impurities.

	Chemical structure	Detected in	NIST match
4		Piperonal	91%
6		Piperonal	70%
5		Piperonal	96%
10		MDP2NP	99%
13		MDP2P, MDMA	96%
14		MDMA	78%

to the NIST database, respectively, and therefore, whilst definite 100% identification is impossible, it is unlikely that they have been improperly assigned. Compound 25 is unusual in that one of the aromatic rings does not contain a methylenedioxy moiety. It is unclear whether these compounds were created during the ionisation process or whether they are in fact relics of unknown rearrangement reactions that occurred during the final chemical reaction step.

The route specific impurities within the prepared piperonal sample included 1-piperidinecarboxaldehyde (4), extended aldehyde (6) and 6-chloropiperonal (5) (Table 3). The chlorinated analogue of piperonal went on to react in an analogous fashion to regular piperonal to give rise to the chlorinated analogues 6-Cl-MDP2NP (10), 6-Cl-MDP2P (13) and 6-Cl-MDMA (14), whilst the extended aldehyde was not found to react in the nitroaldol addition. The chlorinated impurities of the MDMA precursors can be considered valuable fingerprint molecules for this particular synthetic methodology. The compound 2-chloro-4,5-methylenedioxyamphetamine (6-Cl-MDMA) (14) has previously been identified in two forensic analytical studies, one within an illicit batch of ecstasy pills seized within Scotland and the other within a drug user's urine sample in the Czech Republic [23,24]. In both cases it was hypothesised that the chlorinated analogue was a deliberately included adulterant and not an impurity generated during synthesis, however given our results this assumption may have been incorrect. These chlorinated analogues may in fact be route specific impurities of potential diagnostic value.

Owing to the quantity of solvent used and the time consuming nature of the outlined procedure for the production of precursor materials, this synthetic methodology is unlikely to surface in a small-scale clandestine setting. This synthetic route to MDMA may be feasible on an industrial scale, as has been discovered in sophisticated foreign synthesis operations, where the recycling of solvent and spent ruthenium catalyst can be undertaken.

#### 4. Conclusions

Piperonal was successfully prepared from piperine extracted from pepper by a catalytic ruthenium tetroxide oxidation using a variety of co-oxidants and solvent systems. The oxidant that gave the best results, as well as being the most readily available, was the commercially available pool oxidant Oxone® (potassium peroxysulfate). The methodology that was developed is a simple way to synthesise

precursor material with easy to obtain reagents. The crude product for each synthetic step was analysed by GC-MS to provide an impurity profile of the synthetic route. A route specific impurity that arose during the initial oxidation step, 6-chloropiperonal, was found to give rise to chlorinated analogues of each of the synthetic precursors, ultimately giving a trace impurity of 2-chloro-4,5-methylenedioxyamphetamine (6-Cl-MDMA) within the MDMA sample itself. These chlorinated analogues can be considered valuable trace impurities for the identification of which synthetic route was used to produce clandestinely synthesised MDMA.

#### Acknowledgments

Financial support from RMIT University, Melbourne is acknowledged. The authors would like to thank Scott McMaster and Aaron Raynor for their help and troubleshooting, and Paul Morrison for his assistance with mass spectrometry.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scijus.2016.01.003>.

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