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Organic Impurity Profiling of 3,4-Methylenedioxyamphetamine (MDA) Synthesised from Helional

Alexandra L. Mercieca, Harrison C. Fursman, Morgan Alonzo, Scott Chadwick,

Andrew M. McDonagh*

Centre for Forensic Science
School of Mathematical and Physical Sciences
University of Technology Sydney
Broadway NSW 2007
Australia

Corresponding author email: andrew.mcdonagh@uts.edu.au

Contact information: School of Mathematical and Physical Sciences
University of Technology Sydney
Broadway NSW 2007
Australia

Keywords: Helional; impurity profiling, 3,4-methylenedioxyamphetamine; MDA; trichloroisocyanuric acid; “twodogs” method

ABSTRACT

The organic impurity profile of 3,4-methylenedioxyamphetamine (MDA) synthesised from helional via the “twodogs” method was examined to identify route-specific and condition-specific impurities. The synthesis used a condensation reaction, followed by a Beckmann rearrangement, then Hofmann rearrangement, and then conversion to a hydrochloride salt. Two chlorinating agents were investigated for the Hofmann rearrangement reaction, trichloroisocyanuric acid (TCCA) and sodium hypochlorite.

Three route-specific impurities were identified in MDA using TCCA, and two of these impurities were condition-specific such that the impurities that formed were dependent on the alcohol used as solvent. Three additional impurities were identified as non-route-specific as they have previously been identified in MDA synthesised from 3,4-methylenedioxycinnamic acid or piperonal. These non-route-specific impurities were also identified in MDA synthesised using sodium hypochlorite. No impurities were detected in MDA hydrochloride. This study identified route- and condition-specific organic

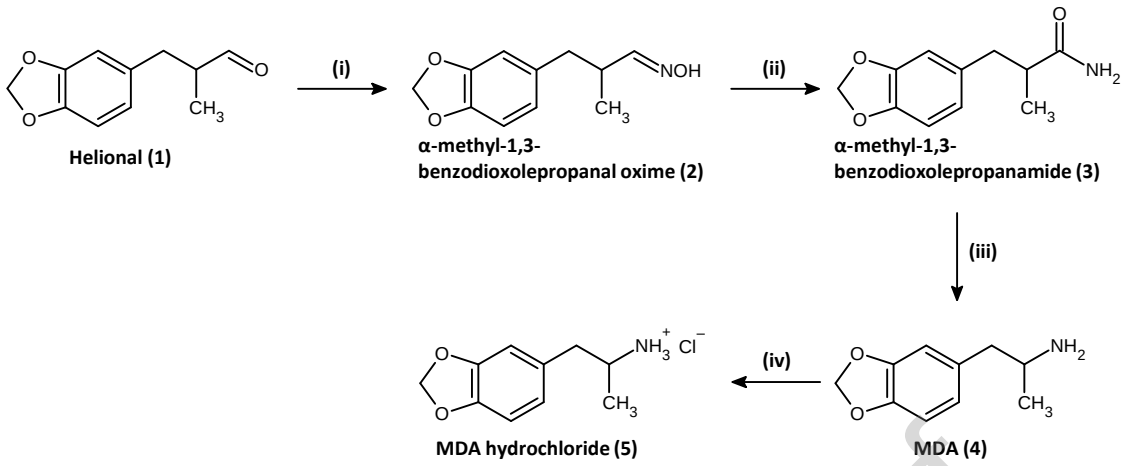
impurities in MDA synthesised via the “twodogs” synthetic route using helional as starting material. The results in this study provide further understanding into the illicit synthesis of MDA and highlight the expanding nature of precursors used for illicit drug manufacture. It provides valuable information to decision makers to enact legislative measures and restrict precursors of concern.

Keywords: Helional; impurity profiling, 3,4-methylenedioxyamphetamine; MDA; trichloroisocyanuric acid; “twodogs” method

1. INTRODUCTION

3,4-Methylenedioxyamphetamine (MDA) is one of many amphetamine-type stimulants (ATS) commonly encountered on the illicit drug market. Similar to 3,4-methylenedioxymethamphetamine (MDMA), MDA exerts hallucinogenic and stimulant effects [1] making it a popular recreational drug [2]. The World Drug Report (2022) reported an increase of 23% in global seizures of MDMA-type stimulants from the 2020 reporting period [3]. MDA can be manufactured illicitly in clandestine laboratories using commercially available precursors and reagents [4]. Reported precursors include safrole, isosafrole and piperonal, with 3,4-methylenedioxyphenylpropan-2-one (MDP2P) as a common synthetic intermediate [4]. The identification of these precursors can be utilised to further understand the clandestine synthesis of drugs and provide decision-makers with usable information to affect change in the availability of precursors of concern.

Organic impurity profiling has been used extensively to examine ATS such as methamphetamine, amphetamine and MDMA to identify precursors and synthetic routes utilised for the clandestine synthesis of drugs [2, 5]. Determination of the route of manufacture of ATS provides key information for forensic intelligence agencies, which in turn can link seizures, track routes of distribution, and identify criminal networks [6]. In the synthesis of MDA from safrole and isosafrole, twenty impurities have been identified in the Leuckart synthetic route, which proceeds via MDP2P and *N*-formyl MDA [7-9], and one in the reductive amination route, which proceeds via MDP2P [8]. The latter study further investigated 3,4-methylenedioxyphenylacetic acid as precursor via both Leuckart and reductive amination routes, finding eight and six impurities, respectively [8]. Twenty impurities have been identified in 2-bromosafrole (from sassafrass oil) which is an intermediate in the bromination-amination route [10]. In the synthesis of MDA from piperonal, eleven impurities were identified in the synthesis via 3,4-methylenedioxyphenyl-2-nitropropene (MDP2NP) [7]. A summary of the route-specific impurities of the aforementioned synthetic routes together with the associated precursors is presented in the supplementary information **(Table S1).**



Scheme 1 *Synthesis of MDA from helional via the "twodogs" method (i) NH_2OH, Na_2CO_3, (ii) $Ni(OAc)_2$, (iii) TCCA or NaOCl, NaOH, (iv) HCl*

Safrole, isosafrole and piperonal have been restricted in many jurisdictions for several years and so new precursors and synthetic routes have emerged. Helional has emerged as a precursor to MDA, with synthetic methods such as the “twodogs” method becoming popular in online forums (**Scheme 1**). Helional is used globally as a component of perfumes as well as in soaps and detergents due to its fresh and watermelon-like fragrance [11]. Given the legitimate use of helional in the perfume industry and the availability and ease at which it can be purchased in bulk, it makes it desirable for clandestine drug manufacturers.

Recent studies have focused on the isotope fractionation of MDA as well as precursors and reagents used during the clandestine synthesis, including helional and hydroxylamine [12]. MDA prepared from helional exhibited isotope fractionation that was observed using isotope ratio-mass spectrometry (IRMS) [11]. The synthetic route produced α-methyl-1,3-benzodioxol-5-propanenitrile as a major organic impurity that formed during the Beckmann rearrangement reaction, however extensive organic impurity profiling was not conducted. The syntheses employed sodium hypochlorite as the oxidising agent for the Hofmann rearrangement step. Online forums have also described an alternative oxidising agent, trichloroisocyanuric acid (TCCA), which is a commercially available pool chlorinating agent. No organic impurity profiling to date has reported the impurities that arise when TCCA or sodium hypochlorite is used for the Hofmann rearrangement during the “twodogs” method.

The results of organic impurity profiling of MDA synthesised from helional via the “twodogs” method using two oxidising agents, sodium hypochlorite and TCCA, are reported here. Route-specific and condition-specific impurities were identified that distinguish the synthetic route from other reported syntheses.

2. MATERIALS AND METHODS

All reactions in the synthesis of MDA hydrochloride from helional using TCCA or sodium hypochlorite were completed a minimum of three times.

2.1 Chemicals

All purchased chemicals were used as received. The following reagents and solvents were purchased from Sigma-Aldrich (Melbourne, Australia): ethyl acetate (high-performance liquid chromatography (HPLC) grade), deuterium oxide (99.9%), chloroform-d (99.8%) with 0.03% TMS, helional (α-methyl-1,3-benzodioxole-5-propanal), hydroxylamine hydrochloride (98%), sodium hypochlorite solution (4-4.99% active chlorine), nickel (II) acetate tetrahydrate, hydrogen chloride solution (2M in diethyl ether) and trichloroisocyanuric acid (90% active chlorine). The following chemicals were purchased from Chem Supply (Gillman, South Australia, Australia): anhydrous sodium sulfate, dichloromethane (methylene chloride), ethyl acetate (analytical reagent grade) and sodium hydroxide (mini pearls). The following chemicals were purchased from various suppliers; helional (Koda Phytorium, Mullumbimby, NSW, Australia), xylenes (Fisher Scientific Company; Fair Lawn, New Jersey, United States), sodium chloride (Rowe Scientific; Wangara, Western Australia, Australia), anhydrous sodium carbonate (Vetec), ethanol and methanol (analytical reagent grade, POCD Scientific; North Rocks, NSW, Australia), hydrochloric acid 32% (ACI Labscan; Bangkok Thailand), Hy-Chlor Tablets for small pools containing 90% w/w trichloroisocyanuric acid (Bunnings Warehouse; Kirrawee, NSW, Australia).

2.2 Synthesis

The compounds described in this section did not undergo rigorous purification procedures (to mimic modestly-equipped clandestine laboratory technique). Thus, the characterisation datasets for each of the synthesised compounds are presented in the supplementary information.

2.2.1 α-Methyl-1,3-benzodioxole-5-propanal oxime

Helional (6.00 g, 31.22 mmol) was dissolved in ethanol (10 mL) and an aqueous solution prepared from sodium carbonate (7.6 mL, 32% w/v, 22.64 mmol) and hydroxylamine hydrochloride (6.6 mL, 49% w/v, 46.91 mmol) was added dropwise using a dropping funnel. The mixture was stirred at room temperature for 19 hours. The reaction mixture was poured into a separating funnel, water (25 mL) was added, and then extracted using dichloromethane (3 x 30 mL). The organic layer washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. Solvent was removed using the rotary evaporator. The crude product obtained was a dark orange transparent oil. Upon standing, the oil crystallised to give a yellow-orange solid (5.97 – 6.30 g).

ATR-FTIR: **Figure S1**. Mass spectrum: **Figure S6**. ^{1}H NMR (400 MHz, $CDCl_3$): **Figure S14**. ^{13}C NMR (101 MHz, $CDCl_3$): **Figure S15**.

2.2.2 α-Methyl-1,3-benzodioxole-5-propanamide

α-Methyl-1,3-benzodioxole-5-propanal oxime (5.00 g, 24.13 mmol) was dissolved in xylene (20 mL) and nickel (II) acetate tetrahydrate (144.14 mg, 0.58 mmol) was added. The mixture was heated under reflux at 140 °C for 5 hours with stirring. After cooling, the solution was transferred to a conical flask and dichloromethane (200 mL) was added. The reaction mixture was divided into four portions, and each were added to de-ionised water (25 mL) and extracted with dichloromethane (2 x 20 mL). The organic layer was washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. The organic layers were combined, and the solvent was removed using a rotary evaporator. The crude product was a light-brown solid. The crude product was purified by triturating with dichloromethane to produce a white fluffy solid (3.82 – 4.88 g). ATR-FTIR: **Figure S2**. Mass spectrum: **Figure S7**. ^{1}H NMR (400 MHz, $CDCl_3$): **Figure S16**. ^{13}C NMR (101 MHz, $CDCl_3$): **Figure S17**.

2.2.3 3,4-Methylenedioxyamphetamine

2.2.3.1 Synthesis using Trichloroisocyanuric acid

α-Methyl-1,3-benzodioxole-5-propanamide (0.4 g, 1.92 mmol) was dissolved in water (14 mL), NaOH (1.45 mL, 10.61 mmol) was added dropwise and left to stir for 15 minutes on ice at 0 °C. Trichloroisocyanuric acid (149.9 mg, 0.65 µmol) was added, and the reaction mixture was left on ice at 0 °C for an additional 1 hour. The reaction mixture was then brought to room temperature, then 75 °C and held for 30 minutes. The reaction mixture was poured into a separating funnel and extracted with dichloromethane (3 x 30 mL). The organic layer was washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. The organic layers were combined, and solvent was removed using the rotary evaporator. When synthesised from crude α-methyl-1,3-benzodioxole-5-propanamide, the final product was a black-brown soil (270.3 – 382.2 mg). When synthesised from purified α-methyl-1,3-benzodioxole-5-propanamide, the final product was a brown transparent oil (286.4 – 351.5 mg). ATR-FTIR: **Figure S3**. Mass spectrum: **Figure S8**. ^{1}H NMR (400 MHz , $CDCl_3$): **Figure S18**. ^{13}C NMR (101 MHz, $CDCl_3$): **Figure S19**.

2.2.3.2 Synthesis using Sodium Hypochlorite

Purified α-methyl-1,3-benzodioxole-5-propanamide (0.4 g, 1.92 mmol) dissolved in water (14 mL), NaOH (1.45 mL, 10.61 mmol) was added dropwise and left to stir for 15 minutes on ice at 0 °C. Sodium hypochlorite solution (6.4 mL, 94.3 mmol) was added, and the reaction mixture was left on ice at 0 °C

for an additional 1 hour. The reaction mixture was then brought to room temperature then 75 °C and held for 30 minutes. The reaction mixture was poured into a separating funnel and extracted with dichloromethane (3 x 30 mL). The organic layer was then washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. The organic layers were combined, and solvent was removed using the rotary evaporator. The final product was a black-brown soil (248.1 – 293.3 mg).^{1}H NMR (400 MHz , $CDCl_3$): **Figure S20**. ^{13}C NMR (101 MHz, $CDCl_3$): **Figure S21**.

2.2.4 3,4-Methylenedioxyamphetamine Hydrochloride

3,4-Methylenedioxyamphetamine (270.3 – 382.2 mg) was dissolved in anhydrous ether (10 mL) with stirring and hydrogen chloride solution (1 mL, 2 M in diethyl ether) was added dropwise. The resultant precipitate was filtered using a Hirsch funnel and washed with diethyl ether. Vacuum suction was applied for a further 5 min to draw air through the solid to assist in drying. When prepared from relatively pure MDA, the final product was an off-white powder (241 – 278.4 mg) and when prepared from the impure brown-black MDA , a brown wax formed. When a wax was formed, the material was triturated with dichloromethane and filtered using a Hirsch funnel to give an off-white powder (13.5 – 90.6 mg). ATR-FTIR: **Figure S5**. ^{1}H NMR (400 MHz, D_2O): **Figure S22**. ^{13}C NMR (101 MHz, D_2O): **Figure S3**.

2.3 Synthesis of Specific Organic Impurities

2.3.1 5-(3,3-Diethoxy-2-methylpropyl)-1,3-benzodioxole

Helional (1.00 g, 5.2 mmol) was dissolved in ethanol (10 mL, 171.26 mmol) with stirring and hydrochloric acid (510 µL, 5.2 mmol, 32% w/v) was added dropwise. The solution was stirred at room temperature for 1 hr. The solution was quenched with saturated sodium hydrogen carbonate and stirred for 2 minutes. The reaction mixture was poured into a separating funnel, de-ionised water (25 mL) was added and the mixture extracted using dichloromethane (3 x 30 mL). The organic layer was then washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered. The solvent was removed using a rotary evaporator. The crude product was purified using flash column chromatography using silica gel 60 (245 nm) and eluted with 1:4 ethyl acetate:hexane. Solvent was removed using a rotary evaporator to give a transparent yellow oil (12 mg). Mass spectrum: **Figure S9**. ^{1}H NMR (400 MHz, $CDCl_3$): **Figure S24**. ^{13}C NMR (101 MHz, $CDCl_3$): **Figure S25**.

2.3.2 3,4-Methylenedioxyamphetamine synthesised in alcoholic solution

Pure α-methyl-1,3-benzodioxole-5-propanamide (0.4 g, 1.92 mmol) was dissolved in water (12.6 mL) and alcohol (methanol or ethanol) (1.4 mL), NaOH (1.45 mL, 10.61 mmol) was added dropwise and

left to stir for 15 minutes on ice at 0 °C. Trichloroisocyanuric acid (149.9 mg, 0.65 µmol) was added, and the reaction mixture was left on ice at 0 °C for an additional 1 hour. The reaction mixture was then brought to room temperature then 75 °C and held for 30 minutes. The reaction mixture was poured into a separating funnel and extracted with dichloromethane (3 x 30 mL). The organic layer was then washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. The organic layers were combined, and solvent was removed using the rotary evaporator. The final product was a brown transparent oil. From methanol: 307.1 mg. From ethanol: 265.7 mg.

2.3.3 N-(1,3-Benzodioxol-5-ylmethylene)-α-methyl-1,3-benzodioxole-5-ethanamine

Pure MDA (100 mg, 0.558 mmol) and piperonal (83.7 mg, 0.558 mmol) were dissolved in water (14 mL) with stirring. The reaction mixture was then brought to 75 °C and held for 30 minutes. The reaction mixture was poured into a separating funnel and extracted with dichloromethane (3 x 30 mL). The organic layer was then washed with de-ionised water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and filtered under vacuum. The organic layers were combined, and solvent was removed using the rotary evaporator. The final product was a yellow - brown transparent oil (104 mg). Mass spectrum: **Figure S10**. ^{1}H NMR (400 MHz, $CDCl_3$): **Figure S26**.

2.4 Instrumentation

2.4.1 Attenuated total reflection – Fourier transform infrared spectroscopy

Attenuated total reflection – Fourier transform infrared (ATR-FTIR) spectra were recorded using a ThermoScientific Nicolet 6700 FT-IR spectrometer equipped with a Smart iTX ATR accessory. Resolution was 6-8 cm^{-1} and the number of scans was 32.

2.4.2 Gas chromatography – mass spectrometry

Gas chromatography – mass spectrometry (GC-MS) was performed using an Agilent 6890 series gas chromatographic system coupled to an Agilent 5973 Network Mass Selective Detector. Analytes were separated using a Zebron ZB-5ms column (30 m x 0.25 mm x 0.25 µm). Helium was used as the carrier gas with a flow rate of 1.0 mL/min. The injection temperature was set to 200 °C and employed a split injection in a 25:1 ratio with 1 µL injections. The oven temperature was programmed at 50 °C maintained for 2 mins followed by a ramp of 10 °C/min to 300 °C and held for 4 minutes. A 3.3 min solvent delay was employed and the total run time was 31 mins. Full-scan mass spectra were collected within the scan range of 30–500 amu. Data was processed and analysed using the GC/MSD ChemStation software (version 01.03.2357). Samples were prepared from 10 mg of analyte in 1 mL of

HPLC grade ethyl acetate, vortexed, then 50 µL was diluted in a further 1 mL of HPLC grade ethyl acetate. A blank of HPLC grade ethyl acetate was run before the 500 ppm analyte.

2.4.3 Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance III spectrometer operating at 400.16 MHz and data were processed using Bruker Topspin software (version 4.1.3). Samples were prepared by dissolving approximately 10 mg in 1 mL of solvent. They were analysed at room temperature (25 °C) and dissolved in deuterated chloroform ($CDCl_3$) or deuterium oxide (D_2O). Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired with a frequency of 400 MHz, spectral width of 8196.72 Hz, relaxation delay of 0.1 s, 32 scans, 3.998 s acquisition time and 30° pulse width. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired with a frequency of 101 MHz, spectral width of 23809.52 Hz, relaxation delay of 2.0 s, 2048 scans, 1.376 s acquisition time and 30° pulse width. Chemical shifts (δ) are reported in ppm and the spectra were calibrated according to the residual solvent chemical shift (^{1}H NMR; $CDCl_3$ = 7.26 ppm and D_2O = 4.79 ppm, ^{13}C NMR; $CDCl_3$ = 77.2 ppm).

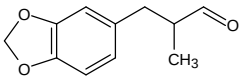
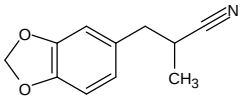
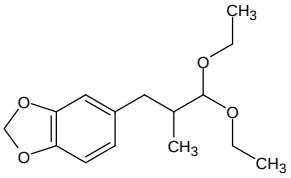
3. RESULTS AND DISCUSSION

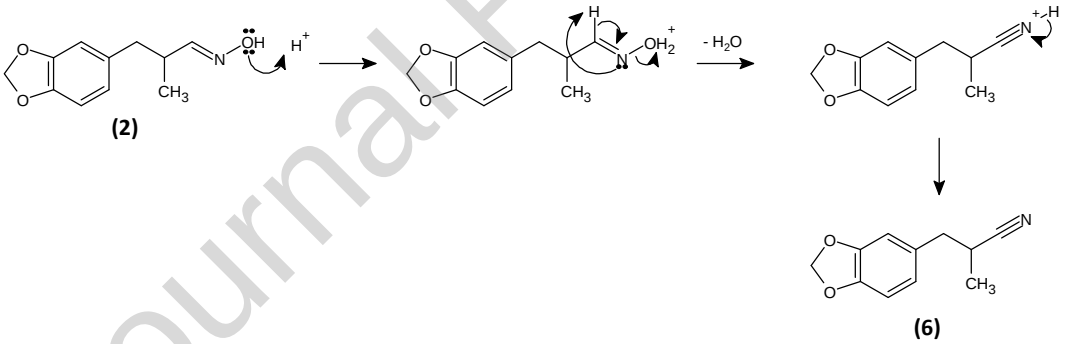
MDA was synthesised five times via the "twodogs" method from helional using TCCA and three times using sodium hypochlorite. The synthetic method and techniques employed were carried out using equipment that could be expected in a modestly equipped clandestine laboratory, demonstrating that the synthetic method is feasible for the illicit manufacture of MDA. Mass spectrometry was used in conjunction with NMR spectroscopy to confirm the structure and identity of the impurities.

3.1 α-Methyl-1,3-benzodioxole-5-propanal oxime

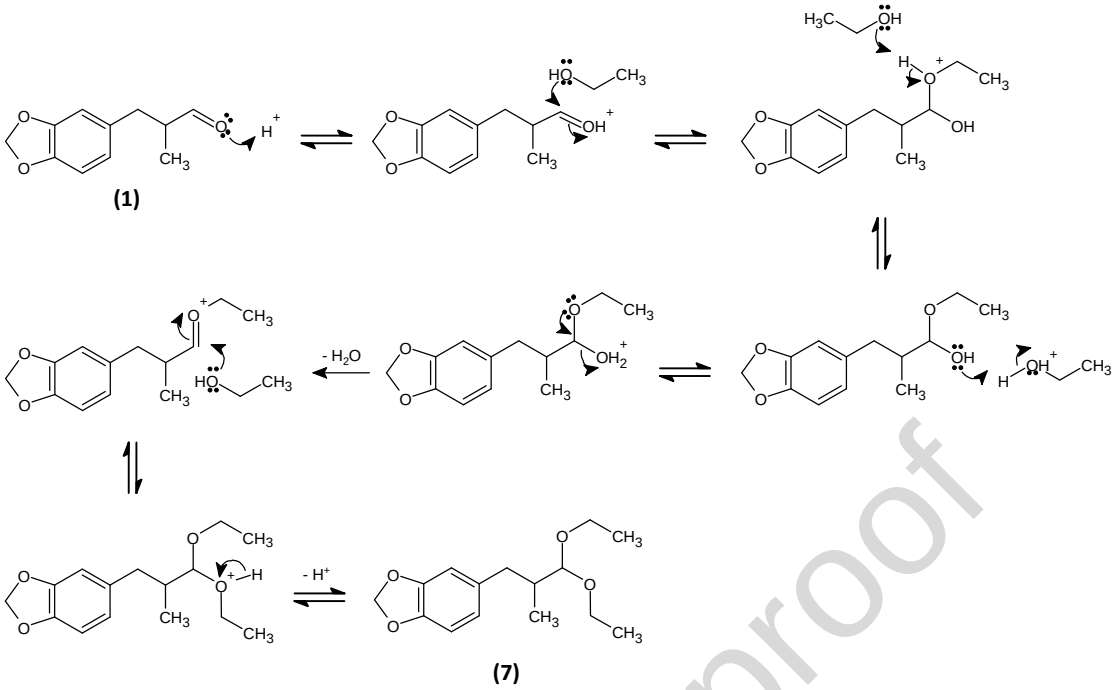
A condensation reaction between helional and hydroxylamine yielded α-methyl-1,3-benzodioxole-5-propanal oxime (**2**). α-Methyl-1,3-benzodioxole-5-propanal oxime (**2**) (a mixture of *E* and *Z* isomers) initially formed as a dark orange, transparent, viscous oil that crystallised upon standing to give a yellow solid. It was synthesised five times from the helional precursor. Three organic impurities were consistently identified across all five iterations (**Table 1** and **Figure S31**).

Table 1 *Impurities identified in α-methyl-1,3-benzodioxole-5-propanal oxime (**2**)*

No.	Impurity Structure	Impurity Name	Identified in iteration				
			1	2	3	4	5
1		Helional	✗	✓	✓	✓	✓
6		α-Methyl-1,3-benzodioxole-5-propanenitrile	✓	✓	✓	✓	✓
7		5-(3,3-Diethoxy-2-methylpropyl)-1,3-benzodioxole	✓	✓	✓	✓	✓



Scheme 2 *Mechanism for the formation of impurity **6***



Scheme 3 *Mechanism for the formation of impurity* ***7***

Impurity **1** is the starting material helional. Its detection is indicative that the reactions (iteration 2-5) did not go to completion. Impurity **6** was identified as α-methyl-1,3-benzodioxole-5-propanenitrile and formed through dehydration of α-methyl-1,3-benzodioxole-5-propanal oxime (**2**) in acidic conditions (**Scheme 2**). Due to the low concentration of the impurity, it was not detected in the ^{1}H NMR spectra of α-methyl-1,3-benzodioxole-5-propanal oxime (**2**). Impurity **6** has been observed previously in isotope fractionation studies as a by-product [11].

Impurity **7**, 5-(3,3-diethoxy-2-methylpropyl)-1,3-benzodioxole, formed from helional and the solvent, ethanol, and H^{+} (**Scheme 3**). This impurity was observed only when a molar excess of hydroxylamine hydrochloride was used relative to sodium carbonate. As the acetal formation is acid catalysed [13], only a small excess of hydroxylamine hydrochloride is required. When excess carbonate was employed, a minor and unidentified impurity was observed.

The interaction between aldehydes and solvents to form acetals or ketals has also been observed in the synthesis of MDA from piperonal [14] and MDMA from catechol and eugenol [15]. In these works, a methoxy ketal derived from MDP2P was observed when methanol was the solvent. In this work, the methoxy analogue of **7**, 5-(3,3-dimethoxy-2-methylpropyl)-1,3-benzodioxole, formed when ethanol was replaced by methanol (see **Figures S32, S11** and **S27**).

3.2 α-Methyl-1,3-benzodioxole-5-propanamide

The formation of α-methyl-1,3-benzodioxole-5-propanamide (**3**) from compound α-methyl-1,3-benzodioxole-5-propanal oxime (**2**) takes place via a Beckmann rearrangement using nickel (II) acetate tetrahydrate as catalyst. α-Methyl-1,3-benzodioxole-5-propanal oxime (**2**) co-ordinates to the nickel centre and dehydrates to form the corresponding nitrile. A second oxime co-ordinates and a five-membered cyclic intermediate forms, which then decomposes to form α-methyl-1,3-benzodioxole-5-propanamide (**3**). α-methyl-1,3-benzodioxole-5-propanamide (**3**) was synthesised five times from the α-methyl-1,3-benzodioxole-5-propanal oxime precursor (**2**). Four organic impurities were identified across all five repeats (**Figure S33**), summarised in **Table 2**.

Table 2 *Impurities identified in the synthesis of α-methyl-1,3-benzodioxole-5-propanamide (**3**)*

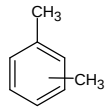
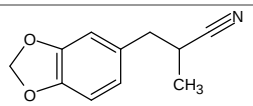
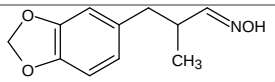
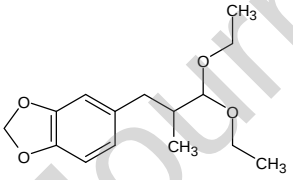
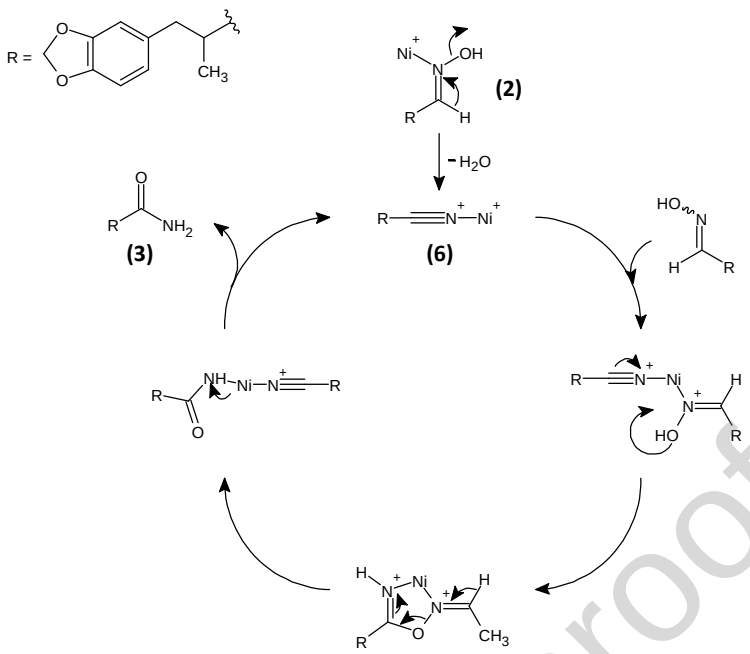
No.	Impurity Structure	Impurity Name	Identified in iteration				
			1	2	3	4	5
8		Xylenes	✓	✗	✗	✗	✗
6		α-Methyl-1,3-benzodioxole-5-propanenitrile	✓	✓	✓	✓	✓
2		α-Methyl-1,3-benzodioxole-5-propanal oxime	✓	✓	✗	✓	✓
7		5-(3,3-Diethoxy-2-methylpropyl)-1,3-benzodioxole	✓	✓	✓	✓	✓

Table 2 shows the four organic impurities identified in the crude amide product. Impurity **8** is xylene, the solvent used for the reaction and was detected only in the first iteration of the synthesis. The presence of solvent in the product is dependent on the thoroughness of solvent removal and so should not be considered an indicator of the synthetic route.



Scheme 4 *Mechanism for the formation of* ***6*** *via the Beckmann rearrangement [16]*

Impurity **6**, α-methyl-1,3-benzodioxole-5-propanenitrile, was previously identified in the synthesis of α-methyl-1,3-benzodioxole-5-propanal oxime (**2**), however, the total ion chromatogram reveals a higher concentration in the synthesis of α-methyl-1,3-benzodioxole-5-propanamide (**3**), the ^{1}H NMR spectrum, **Figure S28**, supports this. The increased concentration of **6** can be attributed to the Beckmann rearrangement (**Scheme 4**) [16]. When no more oxime is present to react or if the reaction does not go to completion, a significant quantity of the nitrile remains. The nitrile, **6**, is essential for the reaction to progress [17] and follows first order kinetics with dependence on the concentration of the nitrile and oxime species. The nitrile species can act as a rate accelerant, increasing the conversion of oxime to amide [16].

Impurity **2** is the previous intermediate, α-methyl-1,3-benzodioxole-5-propanal oxime. Its presence is indicative that the reaction didn't go to completion, possibly due to not enough catalyst being present or slight excess of the starting material used. Impurity **7** was previously identified in the prior step and its identification is indicative that it has carried through this reaction unchanged.

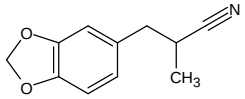
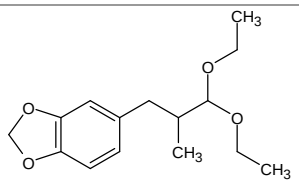
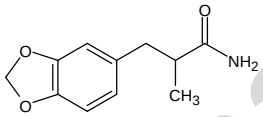
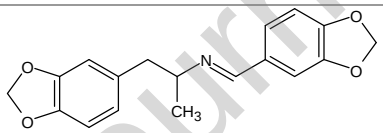
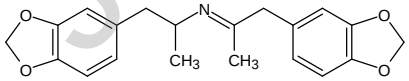
3.3 MDA

The formation of MDA (**4**) from α-methyl-1,3-benzodioxole-5-propanamide (**3**) proceeds via a Hofmann rearrangement. An oxidising agent is required to oxidise α-methyl-1,3-benzodioxole-5-propanamide (**3**) to form the corresponding chloramide, which re-arranges to form an isocyanate intermediate. Loss of carbonyl (as carbon dioxide) gives MDA. In this work, two oxidising agents were explored, TCCA and sodium hypochlorite.

3.3.1 MDA synthesised from α-methyl-1,3-benzodioxole-5-propanamide using TCCA

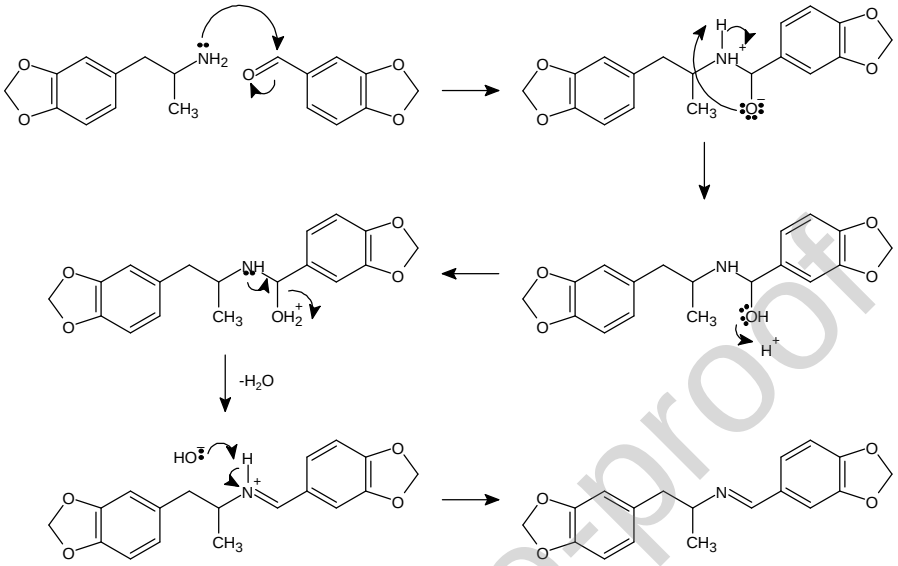
When TCCA was used for the synthesis of MDA (**4**) from crude α-methyl-1,3-benzodioxole-5-propanamide (**3**), five organic impurities were identified across all five iterations (**Table 3** and **Figure S34**). Impurities **6** and **7** formed during the first synthetic step and carried through this reaction unchanged. Impurity **3** is α-methyl-1,3-benzodioxole-5-propanamide, the starting material indicating that the reaction did not proceed to completion.

Table 3 *Impurities identified in MDA (**4**) synthesised from crude α-methyl-1,3-benzodioxole-5-propanamide (**3**) using TCCA*

No.	Impurity Structure	Impurity Name	Identified in iteration				
			1	2	3	4	5
6		α-Methyl-1,3-benzodioxole-5-propanenitrile	✓	✓	✓	✓	✓
7		5-(3,3-Diethoxy-2-methylpropyl)-1,3-benzodioxole	✓	✓	✓	✓	✓
3		α-Methyl-1,3-benzodioxole-5-propanamide	✓	✓	✓	✓	✓
9		*N*-(1,3-Benzodioxol-5-ylmethylene)-α-methyl-1,3-benzodioxole-5-ethanamine	✓	✓	✓	✓	✓
10		*N*-[2-(1,3-Benzodioxol-5-yl)-1-methylethylidene]-α-methyl-1,3-benzodioxole-5-ethanamine	✓	✓	✓	✓	✓

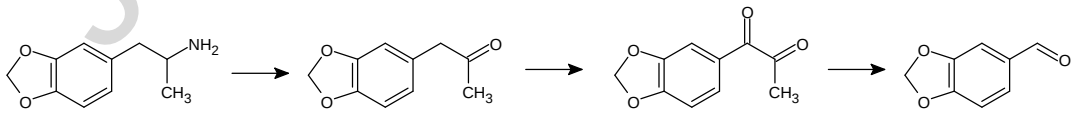
Impurity **9**, *N*-(1,3-benzodioxol-5-ylmethylene)-α-methyl-1,3-benzodioxole-5-ethanamine, has been identified previously in the synthesis of MDA from piperonal via MDP2NP [18] and formed as MDA (**4**) underwent nucleophilic addition to piperonal (**Scheme 5**). This was investigated further using an experiment whereby stoichiometric quantities of pure MDA and piperonal were reacted in water at

75 °C for 30 minutes with **9** identified as the major product (**Figure S35**). Impurity **9** has also been detected in seized MDMA tablets [19].



Scheme 5 *Mechanism for the formation of impurity* ***9***

Impurity **10**, *N*-[2-(1,3-benzodioxol-5-yl)-1-methylethylidene]-α-methyl-1,3-benzodioxole-5-ethanamine, forms by nucleophilic addition of MDA (**4**) to MDP2P as reported previously [20]. Impurity **10** has not been previously reported in the synthesis of MDA from helional but was identified in the synthesis of MDA from piperonal via MDP2NP [18]. The formation of imines from primary amines and ketones during illicit drug synthesis has been discussed in literature [20, 21]. Imines have been identified in the synthesis of amphetamine via the Leuckart synthesis where the major impurity was the condensation product between amphetamine and phenyl-2-propanone, *N*-(β-phenylisopropyl)benzyl methyl ketimine [21].

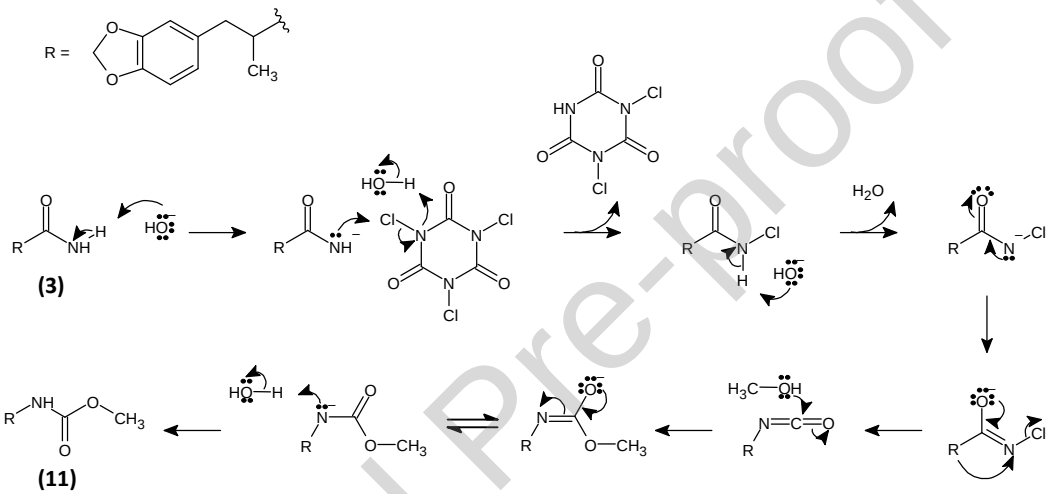


Scheme 6 *Proposed reactions leading to the formation of MDP2P and piperonal*

Importantly, the formation of impurities **9** and **10** requires the prior formation of piperonal and MDP2P although neither were detected in crude MDA (**4**) . It is hypothesised that MDP2P formed during the reaction of MDA (**4**) with TCCA or sodium hypochlorite under basic conditions (others have reported that primary amines can be oxidised to the corresponding ketones using sodium hypochlorite [22]). Subsequently, oxidation of MDP2P to 1-(1,3-benzodioxol-5-yl)-1,2-propanedione followed by

oxidative cleavage gives piperonal (**Scheme 6**). Interestingly, helional has been shown by others to oxidise to MDP2P as well as trace amounts of piperonal and 1-(1,3-benzodioxol-5-yl)-1,2-propanedione [23].

No impurities were detected when MDA (**4**) was synthesised from pure α-methyl-1,3-benzodioxole-5-propanamide (**3**) using TCCA (**Figure S36**). It was found that α-methyl-1,3-benzodioxole-5-propanamide (**3**) reacted completely with TCCA to form relatively pure MDA (**4**). Pure MDA could be achieved in other synthetic routes if the free base is purified so it cannot be unequivocally determined that if pure MDA is obtained, helional is the precursor.



Scheme 7 *Mechanism for the formation of impurity* ***11*** *from compound* ***3***

Methanol has been reported in online forums to aid the solubility of α-methyl-1,3-benzodioxole-5-propanamide (**3**) in water during the Hofmann reaction. When the synthesis of MDA (**4**) was performed in 10% methanol in water, **11**, methyl [1-(1,3-benzodioxol-5-yl)-2-propanyl]carbamate, was detected (**Figure S37, S12** and **S29**). The formation of **11** occurs when the isocyanate intermediate reacts with methanol to form a carbamate (**Scheme 7**) [24]. When the synthesis was conducted using 10% ethanol in place of methanol, the ethyl analogue, ethyl [1-(1,3-benzodioxol-5-yl)-2-propanyl]carbamate was formed (**Figure S38, S13** and **S30**). Similarly, reactions using a 1:1 ratio of water:methanol with benzamide have been reported to form *o*-methyl-*N*-phenyl carbamate [25].

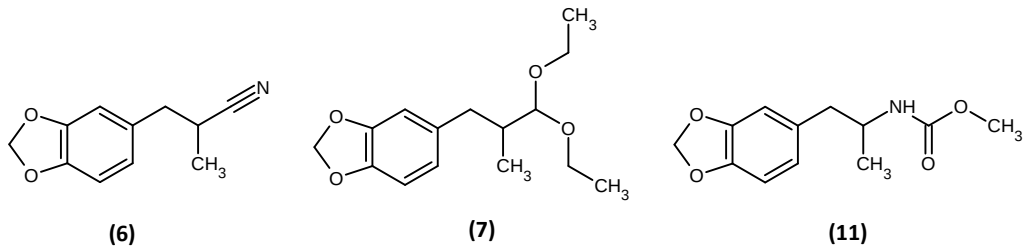
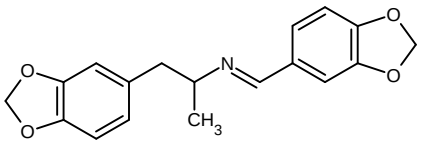
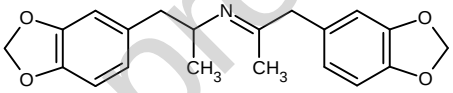


Figure 1 *Route-specific impurities of the "twodogs" method*

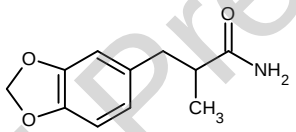
The organic impurity profile of MDA (**4**) synthesised using TCCA from both crude and pure α-methyl-1,3-benzodioxole-5-propanamide (**3**), yielded six impurities. By comparison with other studied synthetic routes to MDA (**4**), three were determined to be route-specific, impurities **6**, **7** and **11** (**Figure 1**). Furthermore, **7** and **11** are condition-specific and depend on whether ethanol or methanol is used. Detection of these impurities in a seized sample of MDA firstly may indicate the "twodogs" method as the method of synthesis and this in turn implicates the reagents used. The identification of the route of synthesis can contribute to criminal intelligence linking seizures and identifying sources of supply. Furthermore, the identification of condition-specific impurities, **7** and **11,** can distinguish between the solvents used in MDA synthesised from helional, based on the different analogues of the impurities that form.



(9)



(10)



(3)

Figure 2 *Non-route-specific impurities of the "twodogs" method*

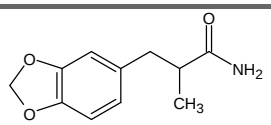
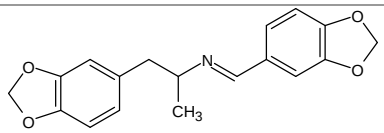
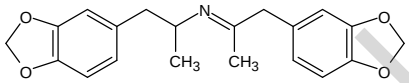
Impurities **3**, **9**, and **10** are not route-specific as they have been identified in other routes to MDA. Impurity **3** is an intermediate in the synthesis of MDA from α-methyl-3,4-methylenedioxycinnamic acid [4] although no impurity profiling has been reported for this synthesis. Both **9** and **10** have previously been characterised as route-specific to the synthesis from piperonal via MDP2NP [18], however, given their detection in MDA via the "twodogs" method, they should not be considered as route-specific. The indication that piperonal and MDP2P form *in situ* suggest that they may also not be route-specific to other syntheses.

3.3.2 MDA synthesised from α-methyl-1,3-benzodioxole-5-propanamide using sodium hypochlorite

When sodium hypochlorite was used for the synthesis of MDA (**4**) from pure α-methyl-1,3-benzodioxole-5-propanamide (**3**) , three organic impurities were identified across three iterations (**Table 4**). Impurity **3** was identified as unreacted starting material in only one iteration. Impurities **9** and **10** are present due to the formation of piperonal and MDP2P *in situ* as a consequence of MDA (**4**) reacting with sodium hypochlorite. Impurities **3**, **9** and **10** were also identified in the synthesis of MDA using TCCA. Given that these impurities are not route-specific, their detection should not be used to

identify helional as the precursor of origin. For the "twodogs" method to be unambiguously identified, additional information outside of illicit drug profiling would need to be employed such as chemicals seized at the crime scene to further substantiate the synthetic route. Furthermore, the change in impurity profile from when TCCA and pure α-methyl-1,3-benzodioxole-5-propanamide are used highlights the versatility of the method and the ways it can be adapted depending on availability of reagents.

Table 4 *Impurities identified in MDA (**4**) synthesised from pure α-methyl-1,3-benzodioxole-5-propanamide (**3**) using sodium hypochlorite*

No.	Impurity Structure	Impurity Name	Identified in iteration		
			1	2	3
3		α-Methyl-1,3-benzodioxole-5-propanamide	✗	✗	✓
9		*N*-(1,3-Benzodioxol-5-ylmethylene)-α-methyl-1,3-benzodioxole-5-ethanamine	✓	✓	✓
10		*N*-[2-(1,3-Benzodioxol-5-yl)-1-methylethylidene]-α-methyl-1,3-benzodioxole-5-ethanamine	✓	✓	✓

3.4 MDA Hydrochloride

No impurities were detected in MDA hydrochloride (**5**) prepared from crude or pure MDA. This was consistent across all samples (**Figure S22**). The lack of detected impurities may be attributed to the method by which MDA hydrochloride (**5**) was synthesised: diethyl ether and dichloromethane are excellent solvents for the removal of organic compounds from the hydrochloride salt (**5**). As no impurities could be detected, analysis of seized MDA hydrochloride could not be used to determine helional as the precursor of origin or that the "twodogs" method was the synthetic route. For helional to be determined as the precursor of origin, the free base or intermediates need to be seized and analysed. Thus, most organic impurity profiling is concerned with analysis of the free base. Previous impurity profiling of MDA from safrole, isosafrole and, piperonal, all report data for the free base only, rather than for the MDA salt [18]. On the other hand, some organic impurity profiling has been reported for MDMA hydrochloride [26], which identified some basic and neutral impurities in the salt (amine impurities constituted most of those detected). Additional analytical techniques would be

required to overcome the shortcomings of organic impurity profiling so that salts of ATS can be used for strategic and operational intelligence within the forensic science community.

CONCLUSION

This work examined the organic impurity profile of MDA synthesised from helional via the "twodogs" method as well as identify the route- and condition-specific impurities that could distinguish this route from other synthetic routes to MDA. The "twodogs" synthetic route consists of a condensation reaction, Beckmann rearrangement, Hofmann rearrangement, and a final conversion of MDA to its hydrochloride salt. Furthermore, two oxidising agents, sodium hypochlorite and TCCA were investigated for the Hofmann rearrangement.

Organic impurity profiling of the intermediates and final product was completed using GC-MS and NMR spectroscopy and several impurities were identified. In α-methyl-1,3-benzodioxole-5-propanal oxime (**2**) , three impurities were identified (**1**, **6**, and **7**) and in α-methyl-1,3-benzodioxole-5-propanamide (**3**) , four impurities were identified (**2**, **6**, **7** and **8**). When MDA (**4**) was synthesised using crude α-methyl-1,3-benzodioxole-5-propanamide (**3**) and TCCA, five impurities were identified (**3**, **6**, **7**, **9**, and **10**), when synthesised using pure α-methyl-1,3-benzodioxole-5-propanamide (**3**) and TCCA no impurities were detected, however, when methanol was used as a solvent, **11** was identified. Synthesis of MDA (**4**) from pure α-methyl-1,3-benzodioxole-5-propanamide (**3**) and sodium hypochlorite yielded three impurities (**3**, **9**, and **10**). Synthesis of MDA hydrochloride (**5**) from both pure and crude MDA yielded no detectable impurities.

Of the impurities identified in MDA, three were determined to be route-specific, impurities **6**, **7** and **11**. Furthermore, **7** and **11** are condition-specific in that the analogue formed correlates to the alcohol used as solvent. Impurities **3**, **9** and **10** are not route-specific and have been identified in other routes to MDA. Impurity **3** is an intermediate in the synthesis from α-methyl-3,4-methylenedioxycinnamic acid and both **9** and **10** have previously been characterised as route-specific to the synthesis from piperonal via MDP2NP. Given no detectable impurities were identified in MDA hydrochloride (**5**), it should not be used for organic impurity profiling. In general, these findings contribute to the knowledge base of the synthesis of MDA and expand awareness of precursors used in illicit manufacture.

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CRediT author statement

Alexandra L. Mercieca: Conceptualization, Methodology, Investigation, Writing - Original Draft.

Harrison C. Fursman: Conceptualization, Methodology, Investigation

Morgan Alonzo: Conceptualization, Writing - Review & Editing

Scott Chadwick: Conceptualization, Methodology, Writing - Review & Editing

Andrew M. McDonagh: Conceptualization, Methodology, Writing - Review & Editing, Supervision

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: