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Synthesis and organic impurity profiling of 4-methoxymethamphetamine hydrochloride and its precursors

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ABSTRACT

4-Methoxymethamphetamine (PMMA) was synthesised from star anise and from 4-methoxytoluene and the organic impurity profiles examined. These two starting materials are unrestricted chemicals in many jurisdictions and contain the requisite functional groups and are thus well suited for clandestine manufacturers. *trans*-Anethole was extracted from star anise and oxidised to 4-methoxyphenyl-2-propanone (PMP2P). 4-Methoxytoluene was oxidised to anisaldehyde, converted to 4-methoxyphenyl-2-nitropropene, and then reduced to PMP2P. The PMP2P obtained by both methods was then converted to PMMA via the Leuckart reaction. 4-Methoxymethamphetamine hydrochloride (PMMA·HCl) was synthesised from PMMA using hydrogen chloride gas. Both of the examined synthetic methods were found to be feasible routes into PMMA·HCl. The products of each step were analysed by gas chromatography–mass spectrometry (GC–MS) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR). Impurities were examined in an attempt to identify route specific compounds, which may provide valuable information about the synthetic pathway and precursors.

1. Introduction

4-Methoxymethamphetamine (or *p*-methoxymethamphetamine, PMMA) is a synthetic substance that is an analogue of methamphetamine and closely related in structure to 3,4-methylenedioxymethamphetamine (MDMA) (Fig. 1) [1]. Drug analogues often appear in the illicit market as substitutes for other substances as well as being marketed in their own right. PMMA is a stimulant with similar [2,3] but possibly more short-lived [4] effects compared to those of MDMA. It has been suggested that there is a small margin between a safe and lethal dose of PMMA [3].

PMMA manufacturers can use synthetic routes adopted from the synthesis of methamphetamine and MDMA. A starting material that is commonly described in the literature is *trans*-anethole (4-methoxyphenyl-2-propene), which is similar in structure to the MDMA precursor isosafrole. Another feasible starting material is anisaldehyde (4-methoxybenzaldehyde), which has a similar structure to the MDMA precursor piperonal and the methamphetamine precursor benzaldehyde. Interestingly, many of the PMMA precursor chemicals can be synthesised or obtained from natural sources and household products. For example, *trans*-anethole is found in star anise oil (>90%), aniseed oil (80–90%) and fennel oil (80%). Alternatively, anisaldehyde can be synthesised from 4-methoxytoluene. The use of uncontrolled precursors such as these by clandestine laboratory operators may significantly reduce the risk associated with detection, and thus be an attractive method of manufacture. In this context, organic impurity profiling is of significant interest to law enforcement agencies as it can provide valuable information about production methods. While there has been a significant amount of research into the organic impurity profiling of many illicit substances such as methamphetamine and MDMA [5,6], there is quite limited information about the impurities that are associated with the synthesis of PMMA [7].

This paper presents the results of organic impurity profiling of 4-methoxymethamphetamine hydrochloride (PMMA·HCl) synthesised from 4-methoxytoluene (Scheme 1, Route 1) and from *trans*-anethole extracted from star anise (Scheme 1, Route 2). These routes are important because they utilise readily available materials and have been reported in freely available literature.

2. Materials and methods

2.1. General

GC–MS analyses were performed using an Agilent 6890 series gas chromatography coupled with an Agilent 5973 network mass

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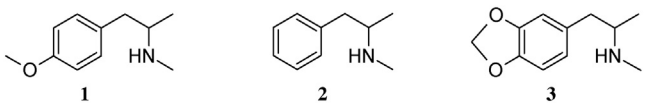


Fig. 1. Structure of PMMA (**1**), methamphetamine (**2**) and MDMA (**3**).

selective detector. The column used was a 30 m long Zebron ZB 5 ms 5% polysilarylene-95% polydimethylsiloxane column, with an internal diameter of 0.25 μm. Helium was used as the carrier gas at 1.0 mL/min. The injection volume and temperature program for PMMA and its precursor was used as followed. The injection volume was 1.0 μL per injection, split mode with a ratio of 13.2:1. The temperature program used was; 50 °C with a 2 min hold time, then ramped at 15 °C per min until 290 °C. The injection volume and temperature program for PMMA hydrochloride was used as followed. The injection volume was 2.0 μL per injection, splitless mode. The temperature program used was; 50 °C held for 1 min, then ramped to 150 °C at 10 °C per min, held for 4 min, ramped at 14 °C per min until 290 °C. Mass spectrometry was performed in positive ionisation mode with a mass spectrum from 29 to 350 amu. The fragmentations listed are for the pure substance only. ^{1}H NMR spectroscopy was performed using an Agilent Direct Drive 500MHz NMR Spectrometer. The machine operated at 499.86 MHz with 64 scans collected. Spectra are available in the Supplementary information files.

2.2. Chemicals

Star anise was purchased from a local grocery store. All purchased chemicals were used as-received. The following chemicals were purchased from AJAX Chemicals: ammonium acetate, copper(II) sulphate, dichloromethane, ethyl acetate, glacial acetic acid, 36% hydrochloric acid, magnesium sulphate (anhydrous), sodium hydroxide and sodium sulphate (anhydrous). The following were purchased from Sigma Aldrich: anisaldehyde, 4-methoxytoluene, *N*-methylformamide, nitroethane and potassium persulfate. The following were purchased from various suppliers: concentrated sulphuric acid (BDH), 28% ammonia solution (Chem-Supply), 30% hydrogen peroxide (Chem-Supply), methanol (Chem-Supply), formic acid (Fluka), iron pin dust (M&B).

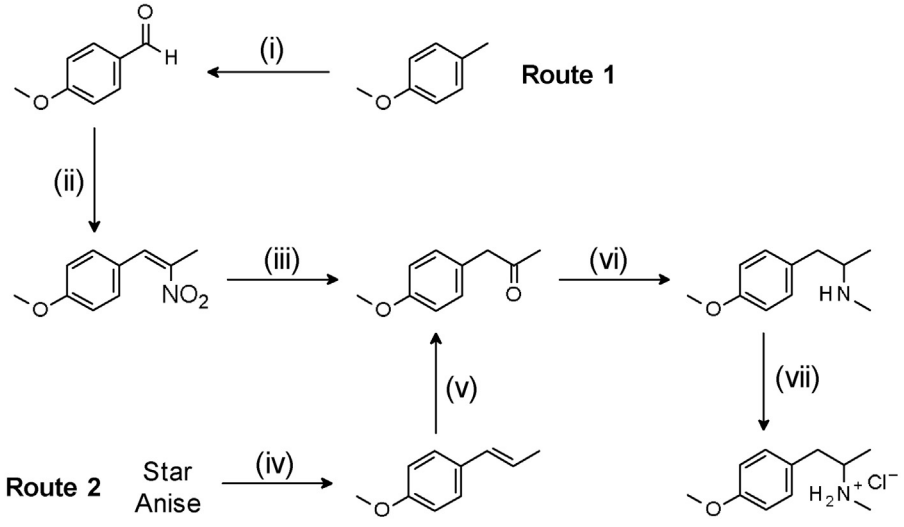
2.3. Synthesis

2.3.1. 4-Methoxyphenyl-2-propanone (PMP2P) from 4-methoxytoluene

2.3.1.1. Synthesis of anisaldehyde. A solution of 4-methoxytoluene (2.250 g, 18.4 mmol) in 70 mL of acetonitrile was added to a mixture of potassium peroxydisulfate (10 g, 37 mmol), copper sulphate (1.0 g, 6.3 mmol) in 70 mL water. The mixture was stirred at 65–70 °C for 3 h and allowed to cool. The product was extracted with 3 × 10 mL of dichloromethane and washed with 10 mL water. The organic extracts were dried over anhydrous sodium sulphate, decanted and concentrated using the rotary evaporator producing a dark orange liquid. Yield: 2.099 g. ^{1}H NMR: Supplementary Fig. S1. GC–MS: Supplementary Fig. S10.

2.3.1.2. Synthesis of 4-methoxyphenyl-2-nitropropene (PMP2NP). Anisaldehyde (1.004 g), nitroethane (2.0 mL, 28 mmol) and ammonium acetate (200 mg, 2.6 mmol) were dissolved in 2.0 mL glacial acetic acid. The mixture was stirred at reflux for 6 h and allowed to cool. Next, water was added and the product was extracted with 2 × 10 mL dichloromethane. The organic extracts were washed with a concentrated sodium hydrogen carbonate solution and water, the dried over anhydrous sodium sulphate. The solvent was removed using the rotary evaporator, producing a dark orange brown liquid. Yield: 1.23 g. ^{1}H NMR: Supplementary Fig. S2. GC–MS: Supplementary Fig. S11.

2.3.1.3. Synthesis of PMP2P. A solution of 4-methoxyphenyl-2-nitropropene (0.800 g) in 20 mL glacial acetic acid was added to a mixture of iron pin dust (2.00 g, 35.8 mmol) in 10 mL glacial acetic acid. The mixture was stirred for 10 min, refluxed for 2 h and allowed to cool. Next, water was added and the mixture was filtered to remove unreacted iron dust pin. The filtrate was extracted with 2 × 10 mL dichloromethane and washed with concentrated sodium hydrogen carbonate solution and water. The organic extracts were dried with anhydrous magnesium sulphate and concentrated using the rotary evaporator, producing a dark brown solid. Yield: 490 mg. ^{1}H NMR: Supplementary Fig. S3. GC–MS: Supplementary Fig. S12.



Scheme 1. Synthesis of PMMA from 4-methoxytoluene (Route 1) and *trans*-anethole extracted from star anise (Route 2). (i) K_2SO_8, $CuSO_4$ (ii) $CH_3CH_2NO_2$, CH_3COONH_4, CH_3COOH (iii) Fe, CH_3COOH (iv) H_2O extraction (v) 1. H_2O_2, HCOOH 2. H_2SO_4 (vi) CH_3NHCHO, HCOOH, HCl (vii) HCl.