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The synthesis and investigation of impurities found in Clandestine Laboratories: Baeyer–Villiger Route Part I; Synthesis of P2P from benzaldehyde and methyl ethyl ketone

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ABSTRACT

The synthesis of impurities detected in clandestinely manufactured Amphetamine Type Stimulants (ATS) has emerged as more desirable than simple "fingerprint" profiling. We have been investigating the impurities formed when phenyl-2-propanone (P2P) **5**, a key ATS precursor, is synthesised in three steps; an aldol condensation of benzaldehyde and methyl ethyl ketone (MEK); a Baeyer–Villiger reaction; and ester hydrolysis**.** We have identified and selectively synthesised several impurities that may be used as route specific markers for this series of synthetic steps. Specifically these impurities are 3-methyl-4-phenyl-3-buten-2-one **3**, 2-methyl-1,5-diphenylpenta-1,4-diene-3-one **9**, 2-(methylamino)-3-methyl-4-phenyl-3-butene **16**, 2-(Methylamino)-3-methyl-4-phenylbutane **17**, and 1-(methylamino)-2-methyl-1,5-diphenylpenta-4-ene-3-one **22**.

1. Introduction

One of the key intermediate molecules synthesised *en route* to the clandestine synthesis of methamphetamine is phenyl-2-propanone (P2P) [1–3], due primarily to the simplicity in which it can be converted into methamphetamine. Due to its significance it is the target molecule of choice for several clandestine synthetic methodologies. One of the more recently reported synthetic routes to P2P reported both in closed [4] and underground [5] literature is known as the Baeyer–Villiger pathway reflecting the procedure used in the second step in the reaction sequence, i.e. a Baeyer–Villiger oxidation. The reaction that bears their names was discovered by Adolf von Baeyer and Victor Villiger in 1899 and is used widely in organic chemistry to transform ketones into esters by the use of peracids or hydrogen peroxide [6].

The Baeyer–Villiger pathway, as it is known, may be used to synthesise methamphetamine **6** in four steps starting from benzaldehyde and methyl ethyl ketone (MEK) as shown in Scheme 1. The first step is an acid catalyzed aldol condensation between benzaldehyde **1** and MEK **2** which forms 3-methyl-4-phenyl-3-buten-2-one **3**. The second step is the Baeyer–Villiger oxidation which forms 2-acetoxy-1-phenyl-1-propene **4** from the reaction between 3-methyl-4-phenyl-3-buten-2-one **3** and peracetic acid (PAA). PAA can either be added directly as a reagent or formed *in situ* from sodium perborate and glacial acetic acid [7]. The third step is the hydrolysis of ester **4** with aqueous sodium hydroxide to form P2P **5**. The final step is a reductive amination of P2P **5** to form methamphetamine **6**.

This paper reports our results from the examination of the reaction conditions for the first two steps in particular, along with the identification and selective synthesis of the various impurities observed in these reactions. In addition, we have examined the compounds that would be formed if impurities produced in these initial reactions were carried through the entire reaction sequence to the formation of methamphetamine.

2. Materials and methods

All reagents were purchased from Sigma–Aldrich (Australia). HCl and H_2SO_4 acids were purchased from ACI Labscan. Solvents were purchased from Sigma–Aldrich and Chemsupply.

2.1. Instrumentation

NMR spectra were recorded on either a Bruker Avance III 600 or 400 MHz NMR spectrometers using $CDCl_3$ as the solvent and

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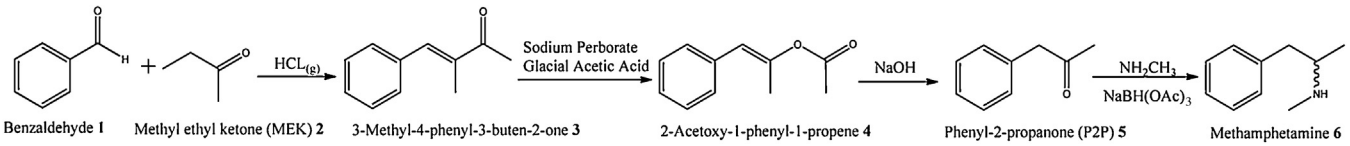

Scheme 1. A four-step reaction sequence, using the Baeyer–Villiger reaction in step 2, used to convert benzaldehyde and MEK into methamphetamine.

internal lock for ^{1}H and ^{13}C spectra. Chemical shifts are recorded in ppm for all spectra. Coupling constants (J values) are recorded in Hz.

GC–MS analysis was performed on a Varian Saturn 2200. Helium was used as the carrier gas at a constant flow of 1.2 mL/min. with a solvent delay of 3 min; the column was Varian DB-5 (5% phenyl methyl polysiloxane) 30 m × 0.25 mm × 0.25 μm film thickness. The spilt ratio was 50:1. The injector temperature was 280 °C, with the initial column temperature at 60 °C for 2.5 min and then ramped at 45 °C per min to 280 °C and held at 280 °C for 12 min. The mass spectrometer operated from 40 to 400 amu electron impact ionisation (EI) with an ionisation energy of 70 eV.

2.2. Synthetic procedures

2.2.1. 3-Methyl-4-phenyl-3-buten-2-one **3**

Hydrogen chloride gas (generated from the reaction between HCl (37%, 25 mL) and H_2SO_4 (98%, 25 mL)) was bubbled though a mixture of benzaldehyde (45 g, 0.43 mol) and MEK (200 mL, 2.23 mol) until the solution turned bright red. The solution was subsequently stirred overnight at room temperature. Water was added and the resulting solution extracted with chloroform then washed with sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed under high vacuum with the remaining liquid distilled (76–78 °C, 0.1 mmHg) yielding a yellow oil which turned brown upon standing. After one day the product had solidified (m.p. 38–42 °C). Yield 73%.

GC: 6.259 min (retention time), MS: 43 (15%), 63 (5%) 91 (7.5%), 115 (55%), 145 (10%), 159 (base peak).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53–7.33 (m, 5H, Ar), 2.417 (s, 3H), 2.07 (d, 3H, J = 1.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.4, 139.8, 137.6, 135.8, 129.7, 128.5, 128.4, 25.8, 12.9.

2.2.2. 2-Methyl-1,5-diphenylpenta-1,4-diene-3-one **9**

NaOH solution (10 mL, 2 M) was added to a mixture of 3-methyl-4-phenyl-3-buten-2-one **3** (2 g, 12.4 mmol) and benzaldehyde (2 g, 18.6 mmol) in ethanol (20 mL) and the resulting solution stirred at room temperature overnight. The mixture was then extracted with chloroform and the extracts dried (Na_2SO_4) prior to removal of the solvent under vacuum. The residue was purified by distillation (175–180 °C, 0.1 mmHg). Yield 87%.

GC: 8.984 min (retention time), MS: 51 (25%), 77 (40%), 91 (25%), 103 (50%), 116 (40%), 131 (50%), 142 (10%), 170 (10%), 205 (15%), 233 (5%), 248 (base peak).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 15.6 Hz), 7.63 (m, 2H), 7.60 (s, 1H)) 7.46–7.35 (m, 9H, Ar), 2.20 (d, 3H, J = 1.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 143.6, 138.8, 138.7, 136.1, 130.3, 129.0, 128.7, 128.6, 128.4, 122.1, 14.0.

2.2.3. 1-Phenyl-1-penten-3-one **8**

NaOH solution (10 mL, 2 M) was added to a mixture of benzaldehyde (4 g, 39 mmol) and MEK (2.8 g, 39 mmol) and the resulting solution stirred at room temperature overnight. The solution was extracted with chloroform, dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by distillation (90 °C, 0.1 mmHg) with the resulting oil solidifying after one day (m.p. 40–41 °C). Yield 50%.

GC: 6.452 min (retention time), MS: 100 (15%), 131 (25%) 161 (base peak).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59–7.40 (m, 6H, Ar-H), 6.78 (d, 1H, J = 16.3 Hz), 2.72 (q, 2H, J = 7.3 Hz), 1.2 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.1, 142.3, 134.6, 130.5, 129, 128.3, 126.1, 34.1, 8.3.

2.2.4. 2-Acetoxy-1-phenyl-1-propene **4**

Sodium perborate (5 g, 32 mmol) was added portion-wise over 6 h to a mixture of 3-methyl-4-phenyl-3-buten-2-one **3** (2 g, 14 mmol), glacial acetic acid (7 mL, 0.122 mol), and acetone (4 mL) at 55 °C. The solution was heated under reflux at 55 °C for a total of 24 h. Upon cooling to room temperature, water (20 mL) was added followed by extraction with chloroform. The organic solution was dried (Na_2SO_4) and the solvent removed under vacuum. **4** was used in the subsequent hydrolysis without any further purification, crude yield 80%.[1]

GC: 6.053 min (retention time), MS: 43 (15%), 91 (20%), 133 (base peak), 176 (10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5H, Ar), 6.24 (s, 1H), 2.16 (s, 3H), 2.10 (d, 3H, J = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 147.9, 134.9, 128.8, 128.3, 126.96, 118.8, 21.1, 17.1.

2.2.5. 2-Acetoxy-1-phenyl-1-propene **4** (Baeyer–Villiger reaction using SARD-Oxy plus)

SARD-oxy plus (3 g, 2–6 mmol of sodium percarbonate) was added portion-wise over 6 h to a mixture of 3-methyl-4-phenyl-3-buten-2-one **3** (0.5 g, 3 mmol), glacial acetic acid (7 mL, 0.122 mol), at 55 °C. The solution was heated under reflux at 55 °C for a total of 24 h. Upon cooling to room temperature, brine was added followed by extraction with chloroform, which was then washed with brine. The organic solution was dried (Na_2SO_4) and the solvent removed under vacuum. Yield 43% based on ^{1}H NMR.[2]

2.2.6. 1-Chloro-1-phenyl-2-propanone (1-chloro-P2P) **15** (by-product from the Baeyer–Villiger reaction using SARD-Oxy plus)

Yield 21% from ^{1}H NMR,‡ GC: 5.713 min (retention time), MS: 43 (base peak), 63 (15%), 89 (30%), 105 (10%), 125 (50%), 133 (15%), ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.24 (m, 5H, Ar), 5.26 (s, 1H), 2.13 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.1, 129.2, 192.1, 127.9, 66.6, 27.8.

2.2.7. Phenyl-2-propanone (P2P) **5**

A mixture of 2-acetoxy-1-phenyl-1-propene **4** (0.9 g, 5 mmol) and aqueous sodium hydroxide (5 mL, 2 M) was stirred at 50 °C overnight. The solution was then extracted with chloroform, the organic solution dried (Na_2SO_4) and the solvent removed under vacuum. Yield 80% over two steps from **3**.

GC: 5.261 min (retention time), MS: 43 (25%), 65 (15%), 91 (30%), 135 (base peak).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H, ArH), 3.7 (s, 2H), 2.16 (s, 3H).

[1] Crude yield was determined from the mass of impure material, in comparison to yield which was calculated from the mass of purified compound.

[2] Yield from ^{1}H NMR is based on the relative integration for the methyl group resonances of major compounds in the reaction mixture.