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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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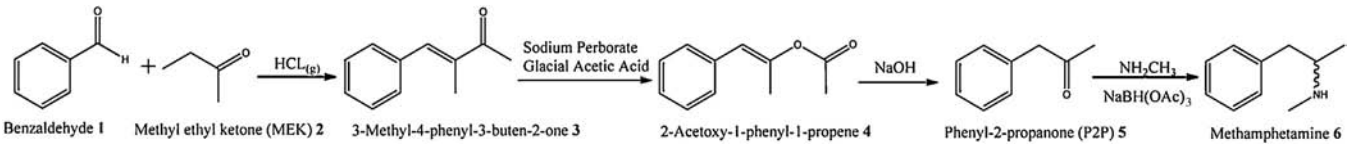


Scheme 1. A four-step reaction sequence, using the Baeyer–Villiger reaction in step 2, used to convert benzaldehyde and MEK into methamphetamine.

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.

*2.2.8. Methamphetamine **6***

A mixture of P2P **5** (0.1 g, 0.75 mmol) and methylamine (33% in ethanol, 0.21 g, 2.29 mmol) in THF (5 mL) was added dropwise to $NaBH(OAc)_3$ (0.312 g, 1.49 mmol) then glacial acetic acid (0.090 g, 5.97 mmol) was added dropwise at 0 °C. The solution was then heated to 55 °C for 2 h, followed by cooling to room temperature. Water was added, the solution basified with NaOH solution (2 M) and then extracted with ether. The ether solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. Yield 85%.

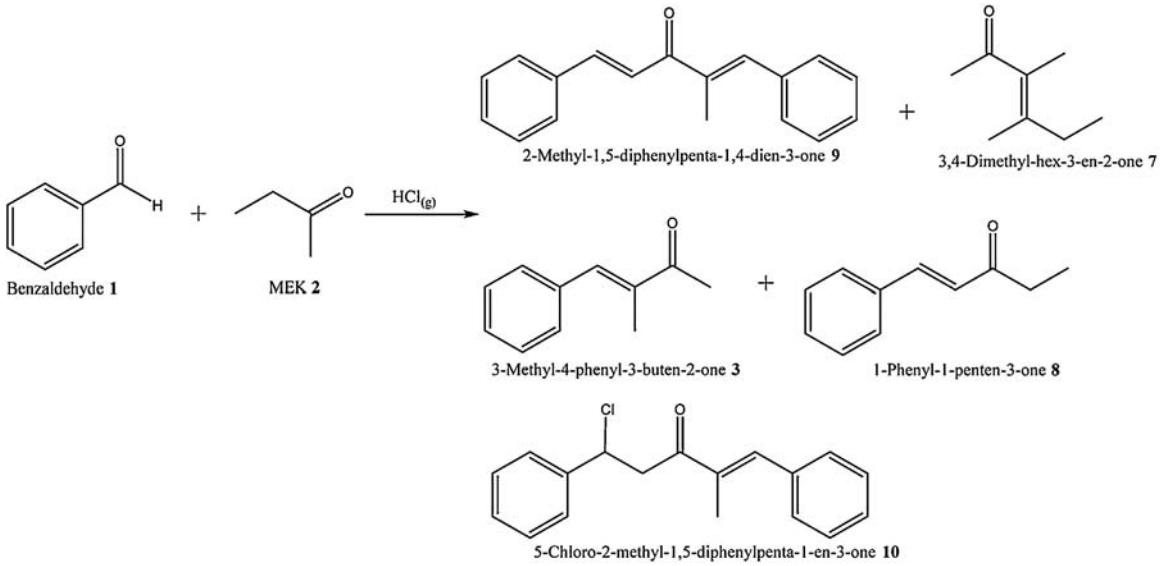


Fig. 1. Outlines the first step in the Bayer-Villiger pathway, an aldol condensation, and several of the by-products formed in the reaction.

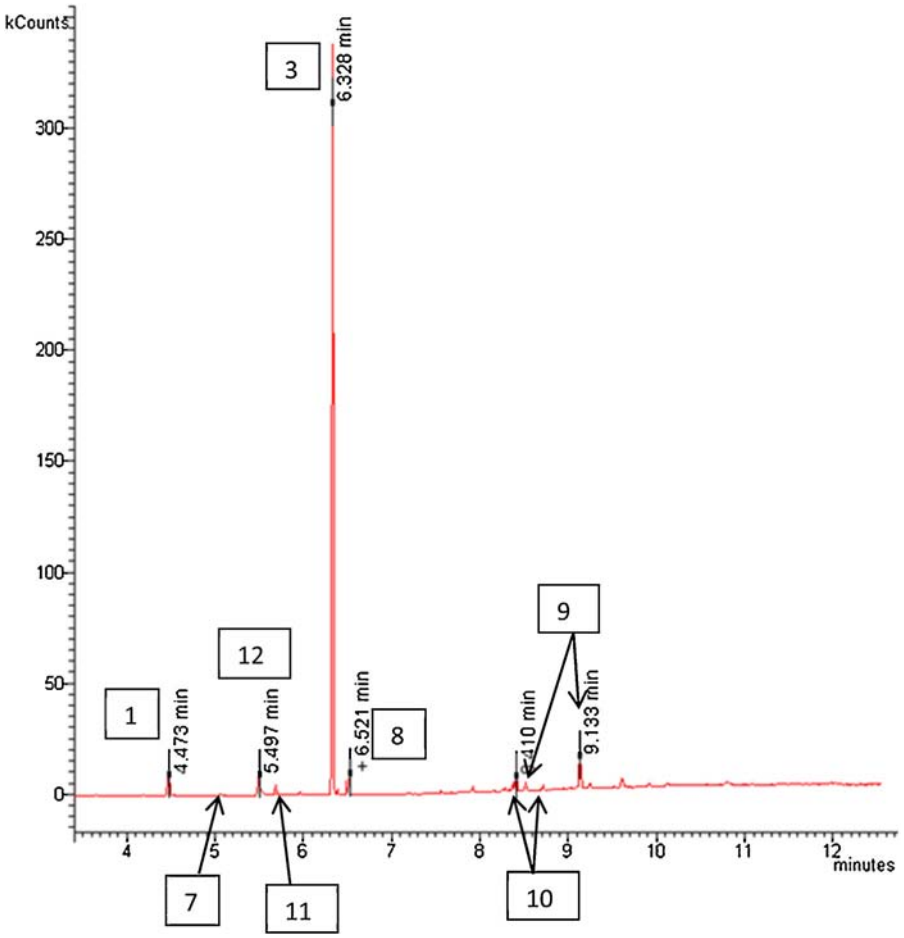


Fig. 2. Partial GC–MS trace of reaction mixture showing by-products from the aldol condensation reaction using six equivalents of MEK.

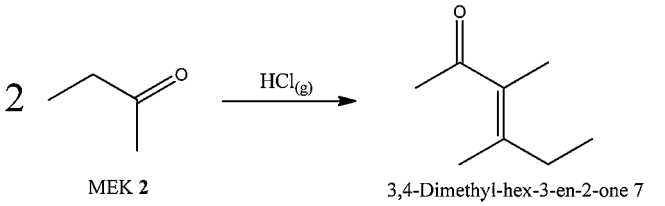


Fig. 3. Self-aldol condensation of MEK with gaseous hydrogen chloride to selectively synthesise **7**.

GC: 5.48 min (retention time), MS: 42 (5%), 58 (base peak), 65 (5%), 91 (10%) 150 (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.13 (m, 5H, ArH), 2.80–2.65 (m, 2H), 2.57 (distorted d, J = 6.2, 6.9 Hz, 1H), 2.35 (s, 3H), 1.02 (d, J = 6.2 Hz, 3H).

Reductive amination reactions on compounds **3**, **8**, **9** were carried out using the same method as outlined above for P2P and purified by column chromatography (silica).

*2.2.9. 2-(Methylamino)-3-methyl-4-phenyl-3-butene **16** (reductive amination reaction on compound **3**)*

GC: 6.215 min (retention time), MS: 42 (10%), 58 (40%), 91 (20%), 115 (10%), 129 (15%), 145 (20%), 160 (base peak), 175 (30%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.13 (m, 5H, ArH), 6.52 (s, 1H), 3.48 (q, 1H, J = 6.7) 2.47 (s, 3H), 1.84 (s, 3H), 1.47 (d, 3H, J = 6.7). ^{13}C NMR (150 MHz, $CDCl_3$): δ 128.8, 128.6, 128.0, 127.7, 127.1, 70.6, 51.1, 41.2 11.1.

*2.2.10. 3-(Methylamino)-1-phenylpent-1-ene **20** (reductive amination reaction on compound **8**)*

GC: 6.394 min (retention time), MS: 72 (5%), 91 (20%), 115 (10%), 146 (base peak), 175 (5%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5, ArH), 6.6 (d, 1H, J = 16 Hz) 6.1 (dd 1H, J = 15.8, 6.6), 2.5 (s, 3H), 2.2 (m, 1H) 1.84 (m, 2H, J = 7.0), 0.97 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 133.7, 129.0, 128.7, 128.4, 126.8, 136.4, 64.9, 29.7, 14.1, 10.3.

*2.2.11. 1,3-Di(methylamino)-1-phenylpentane **21** (reductive amination reaction on compound **8**)*

Isolated as a mixture of diastereomers.

GC: 6.672 min (retention time), MS: 42 (35%), 75 (10%), 120 (base peak), 146 (10%) 174 (20%), 194 (50%) 207 (45%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.211 (m, 10H, ArH), 3.96 (m, 1H), 3.80 (m, 1H) 3.69 (m, 2H), 2.36 (s, 3H), 2.25 (s, 3H), 1.87 (m, 2H), 1.74 (m, 2H) 1.64 (m, 1H), 1.54 (m, 2H), 1.45 (m, 2H), 0.94 (t, 3H, J = 7.5 Hz) 0.87 (t, 3H, J = 7.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): 128.5, 127.5, 127.5, 126.9, 126.5, 74.2, 70.3 65.7, 62.7 42.5, 40.7, 33.7 33.2, 30.9, 30.1, 10.1, 9.8.

*2.2.12. 1-(Methylamino)-2-methyl-1,5-diphenylpenta-4-ene-3-one **22** (reductive amination on compound **9**)*

Isolated as a mixture of diastereomers.

GC: 8.438 min (retention time), MS: 42 (30%), 51 (15%) 77 (35%), 91 (35%), 104 (60%), 118 (base peak), 120 (80%), 131 (20), 146 (65%), 202 (20%), 222 (5%), 279 (40%).

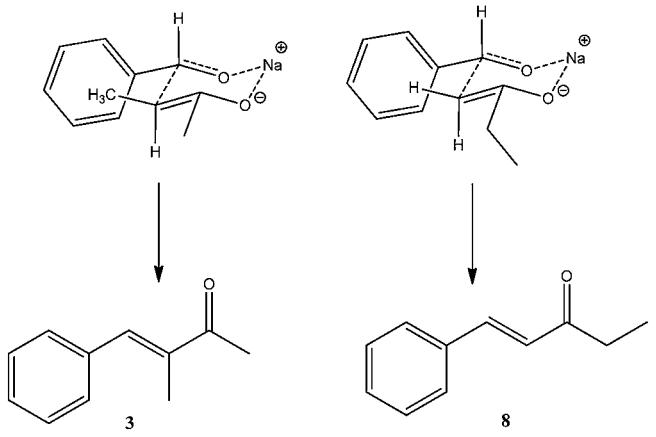


Fig. 5. Various chair transition states for the base catalysed aldol reaction.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.26 (m, 12, ArH), 3.4 (dd, 1H, J = 12.2, 3.3 Hz), 2.98 (d, 1H, J = 10.6 Hz), 2.84 (m, 1H), 2.55 (dd, 1H, J = 3.2, 13.8 Hz), 1.75 (s, 3H), 0.75 (d, 3H, J = 6.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.7, 162.5, 143.4, 142.3, 130.5, 128.8, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.0, 77.4, 70.7, 51.1, 50.9, 41.2, 11.1.

*2.2.13. 2-(Methylamino)-3-methyl-4-phenylbutane **17***

A mixture of 3-methyl-4-phenyl-3-buten-2-one **3** (0.5 g, 3.1 mmol), methylamine (33% in ethanol, 0.32 g, 4.7 mmol) and glacial acetic acid (0.19 g, 3.1 mmol) was stirred at room temperature for 1 hour. $Pd(OH)_2/C$ (20%, 0.5 g, 0.47 mmol) was added to the mixture which was stirred for 5 h at room temperature under an atmosphere of hydrogen (1 atm, balloon). Water was added, the solution basified with NaOH solution (2 M) and then extracted with ether. The ether solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. The amine **17** and ketone **19** major products were isolated and separated by liquid-liquid extraction.

*2.2.14. 2-(Methylamino)-3-methyl-4-phenylbutane **17***

Isolated as a mixture of diastereomers. Yield 30%.

GC: 6.11 min (retention time), MS: 43 (5%), 56 (5%), 58 (base peak), 65 (10%), 91 (20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.15 (m, 10H, ArH), 2.88 (dd, 1H, J = 13.2, 4.7 Hz), 2.68 (dd, 1H, J = 13.5, 5.9 Hz), 2.56 (m, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 2.29 (dd, 1H, J = 13.3, 9.9 Hz), 1.98 (m, 1H), 1.89 (m, 1H), 1.07 (d, 3H, J = 6.6 Hz) 1.05 (d, 3H, J = 6.5 Hz) 0.85 (d, 3H, J = 3.7 Hz) 0.83 (d, 3H, J = 3.7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 1.41.5, 140.9, 129.2, 129.0, 128.3, 128.2, 125.9 125.7, 59.0, 58.3, 40.4, 39.4, 38.4, 38.1 34.0, 33.6, 15.7, 15.4, 14.1, 13.5.

*2.2.15. 3-Methyl-4-phenyl-3-butan-2-one **19***

Yield 35%.

GC: 5.81 min (retention time), MS: 43 (35%), 65 (10%), 77 (5%), 91 (base peak), 119 (25%), 129 (5%), 147 (55%), 161 (35%).

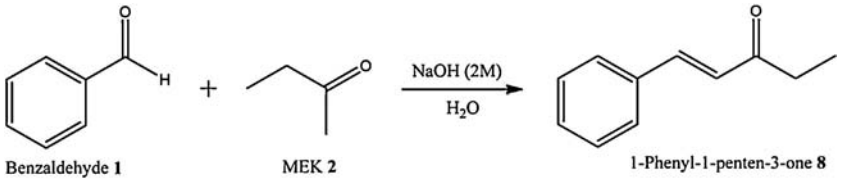


Fig. 4. Base catalysed aldol condensation between benzaldehyde and MEK to yield **8**.

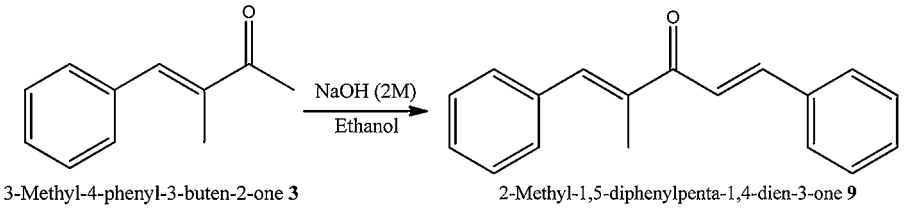


Fig. 6. Aldol condensation of **3** for the selective synthesis of **9**.

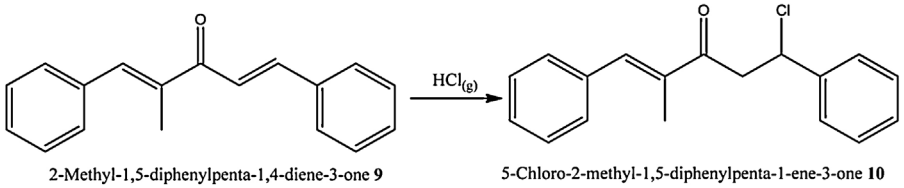


Fig. 7. Reaction between 2-methyl-1,5-diphenylpenta-1,4-diene-3-one **9** and HCl gas.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.15 (m, 5H, ArH), 3.01 (dd, 1H, J = 13.7, 6.8), 2.84 (m, 1H,), 2.57 (dd, 1H, J = 13.7, 7.8 Hz), 2.01 (s, 3H), 1.09 (d, 3H, J = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2. 139.7, 128.9, 128.4, 126.3, 48.3, 38.9, 28.9, 16.2.

3. Results and discussion

3.1. The aldol reaction

The first step in the Baeyer–Villiger pathway is an aldol condensation between benzaldehyde and MEK to form 3-methyl-4-phenyl-3-buten-2-one **3** as shown in Fig. 1. The product distribution is dependent on the amount of MEK used (*vida infra*) which in the current example was six equivalents. In this case the aldol reaction is acid catalysed via bubbling dry hydrogen chloride gas through the solution. The dry gas is needed due to the equilibrium involved in the dehydration step of the aldol reaction giving the alkene product. After reaction workup the organic material was subjected to analysis by GC–MS, the results of which are shown in Fig. 2 with compound structures shown in Table 1. Clearly evident is the fact that the aldol product **3** is the major material present with only very minor levels of impurities observed. Also shown in Fig. 1 are several by-products that have been observed in the GC–MS analysis. In particular, **7** which comes from the self-aldol reaction of MEK, **8** which is a regioisomer of adduct **3**, **9** from a second aldol reaction of adduct **3** and **10** which is a chloro derivative of **9**. Overall these impurities are only formed in very minor amounts and the major product from the reaction is the desired aldol product **3**.

The aldol adduct **3** is able to exist as two isomers, namely *cis* and *trans*, about the double bond with the *trans*-isomer expected to be the thermodynamically more stable. These isomers are unable to be distinguished by MS, however analysis using nuclear Overhauser effect spectroscopy (NOESY) ^{1}H NMR confirmed the *trans*-geometry of **3**. In addition, molecular modelling at DFT level shows the *trans*- isomer is approximately 15 kJ mol^{-1} more stable than the *cis*-isomer. Returning to the GC–MS trace in Fig. 2 we can now state that the *trans*-isomer is the major isomer detected with only trace amounts of the *cis*-isomer **11** being formed.

Having identified the various compounds formed in the aldol reaction using GC–MS we set about selectively synthesising each of them to verify their identify as well as to allow for complete characterisation (e.g. mp, bp, NMR spectra).

3.2. Targeted synthesis of identified by-products

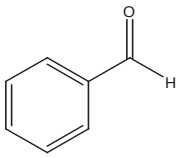
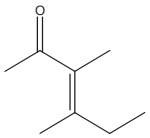
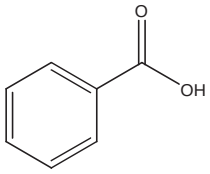
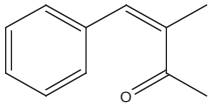
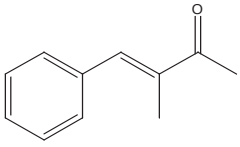
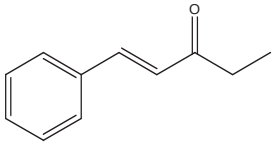
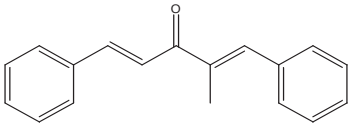
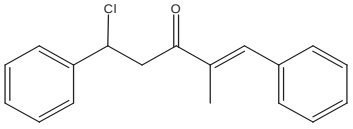
As part of our research we have been attempting to not only identify by-product impurities but also to independently synthesise as many of these compounds as possible. In this case the first compound targeted was the aldol self-condensation product of MEK namely **7**. Thus MEK was treated with gaseous hydrogen chloride which allows selective formation of the self-condensation adduct (Fig. 3). This aldol reaction produces several isomers of **7** including regioisomers and *cis*/*trans* isomers. The identity of **7** was confirmed using GC–MS and NMR spectroscopy.

Another impurity that was observed in the original reaction was aldol adduct **8** formed by reaction through the methyl group of MEK rather than the ethyl group that yields **3**. Adduct **8** was able to be selectively synthesised using a base catalysed aldol reaction between benzaldehyde and MEK (2 M NaOH in water) (Fig. 4) and proceeded in 50% yield. This complete reversal of regioselectivity is dependent on the aldol condensation being acid or base catalysed. Under acidic conditions the most substituted enol is significantly more stable and which results in the selective formation of **3** (molecular modelling at DFT level shows the enol is 9 kJ mol^{-1} more stable). Under basic conditions however the most substituted enol is not significantly more stable (1 kJ mol^{-1}). In this case we have ascribed the selective formation of **8** to steric interaction in the transition state. Under basic conditions the reaction proceeds through a chair transition state which has the two oxygen atoms bridged by a sodium ion. The chair transition state leading to **8** has less steric interaction between the aromatic ring and the carbon chain of MEK (molecular modelling at DFT level shows the transition state is 8.3 kJ mol^{-1} more stable). Fig. 5 shows the chair transition states leading to **3** and **8** under basic conditions.

The next by-product to be targeted for synthesis was the bis-aldol adduct **9**, which presumably forms in the original reaction mixture as a result of a second aldol reaction of adduct **3**. However, treatment of adduct **3** with benzaldehyde and gaseous hydrogen chloride (in line with the original reaction conditions) yielded only 20%[3] of adduct **9**. In this case use of basic conditions (NaOH, 2 M) proved to be effective in forming **9** from **3** and benzaldehyde in 87% yield (Fig. 6). The reaction was found to be stereoselective since only one isomer of **9** was produced in the reaction which was determined to be the *trans*-*trans*-isomer from the large coupling constant of 15.6 Hz between olefinic protons observed in the

[3] 20% yield was estimated from the integration of the GC-MS traces of **9** compared to all other signals in the GC–MS chromatogram.

Table 1
Numbers and structures for compounds used in Fig. 2.

Compound number	Compound	Chemical formula	Mass spectrum data
1	 Benzaldehyde	Chemical formula: C_7H_6O Exact mass: 106.64	51 (10%), 77(25%), 105(base peak)
7	 3,4-Dimethyl-hex-3-en-2-one	Chemical formula: $C_8H_{14}O$ Exact mass: 126.10	43 (base peak), 55 (30%), 69 (40%), 83 (30%), 111 (45%) 126 (45%)
12	 Benzoic acid	Chemical formula: $C_7H_6O_2$ Exact mass: 122.04	51 (25%), 77(50%) 105 (95%) 122 (base peak)
11	 *Cis*-3-Methyl-4-phenyl-3-buten-2-one	Chemical formula: $C_{11}H_{12}O$ Exact mass: 160.09	43 (15%), 63 (5%) 91 (7.5%), 115 (55%), 145 (10%), 159 (base peak)
3	 *trans*-3-Methyl-4-phenyl-3-buten-2-one	Chemical formula: $C_{11}H_{12}O$ Exact mass: 160.09	43 (15%), 63 (5%) 91 (7.5%), 115 (55%), 145 (10%), 159 (base peak)
8	 1-Phenyl-1-penten-3-one	Chemical formula: $C_{11}H_{12}O$ Exact Mass: 160.09	100 (15%), 131 (25%) 161 (base peak)
9	 2-Methyl-1,5-diphenylpenta-1,4-dien-3-one	Chemical formula: $C_{18}H_{16}O$ Exact mass: 248.12	51 (25%), 77 (40%), 91 (25%), 103 (50%), 116 (40%), 131 (50%), 142 (10%), 170 (10%), 205 (15%), 233 (5%), 248 (base peak)
10	 5-Chloro-2-methyl-1,5-diphenylpenta-1-en-3-one	Chemical formula: $C_{18}H_{17}ClO$ Exact mass: 284.10	51 (15%), 78 (15%), 104 (30%), 115 (36%), 152 (55%), 249 (base peak), 284 (75%), 286 (25%)

^{1}H NMR. The partial GC–MS trace of the original reaction mixture in Fig. 2 shows two peaks that may be assigned to 2-methyl-1,5-diphenylpenta-1,4-diene-3-one **9** presumably as a result of *cis*- and *trans*- isomers from the newly formed pi bond.

The final by-product targeted for synthesis was 5-chloro-2-methyl-1,5-diphenylpenta-1-en-3-one **10**. The formation of this product may be envisaged to occur via several different pathways: (i) via an SN_1 reaction from the intermediate hydroxyl compound

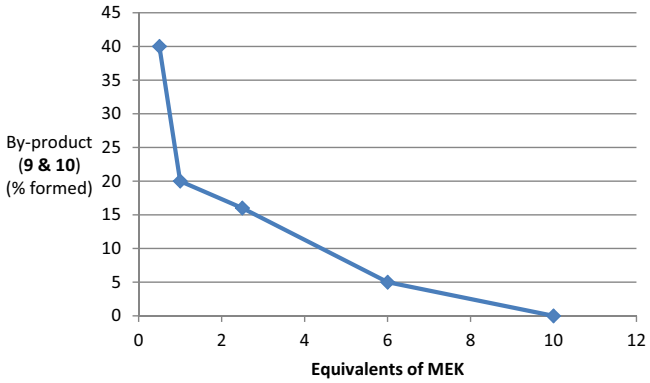


Fig. 8. Graph showing the approximate amount of **9** and **10** which are formed in the aldol condensation reaction (by GC–MS) versus the equivalents of MEK used.

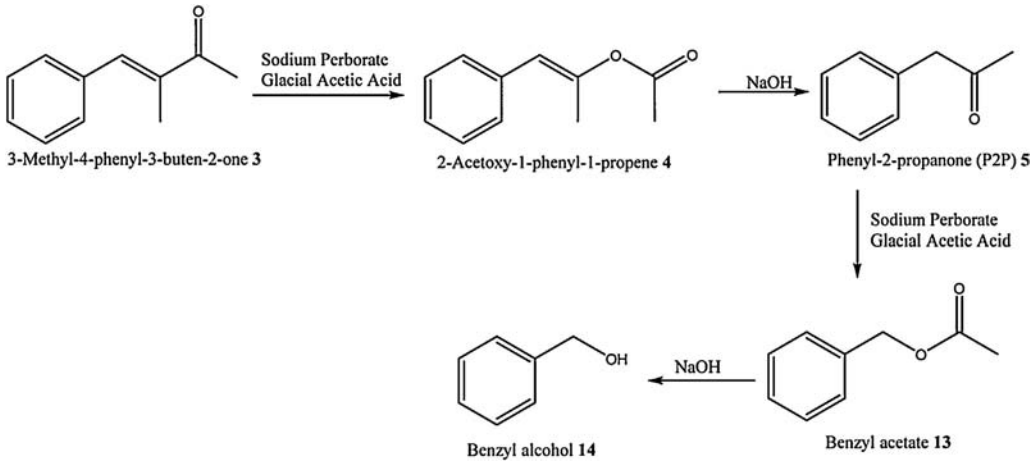


Fig. 9. Baeyer–Villiger reaction pathway and several of the by-products formed in the reaction sequence.

before it dehydrates to form **9**, (ii) addition of HCl across the pi bond of **9**, or (iii) conjugate addition of chloride to **9** followed by protonation. The reaction between 2-methyl-1,5-diphenylpenta-1,4-diene-3-one **9** and HCl gas, as shown in Fig. 7, was performed but only trace amounts of **10** were observed by GC–MS with the major material present being **9**. The synthesis of **10** was not pursued further.

3.3. Variations to the initial reaction conditions

Having identified the major by-products formed in the initial aldol reaction of the Baeyer–Villiger pathway we decided to investigate the effect of changing the original reaction conditions would have on the by-product distribution. The motivation behind this was the clandestine cooks desire to: (i) utilise chemicals at hand, and (ii) maximise the use of hard-to-obtain chemicals, which may result in sub-stoichiometric quantities of materials being used in reactions. Toward this end we undertook variations in the acid catalyst used in the aldol reaction as well as the equivalents of MEK used in the reaction.

Table 2
Effects of different acids in the aldol condensation between benzaldehyde and MEK.

Acid	Result
HCl gas	**3** isolated in 75% yield
37% $HCl_{(aq)}$ (4 mol. %)	Very slow reaction, trace amounts of **3** formed
37% $HCl_{(aq)}$ (one equiv.)	**3** formed in 35%[a]
98% sulphuric (6 mol %.)	**3** formed in 30%[a]
98% sulphuric (two equiv.)	**3** isolated in 40% yield
Glacial Acetic acid	No product detected
Trifluoroacetic acid	No product detected
Toluene-4-sulfonic acid	Slowly oxidised benzaldehyde to benzoic acid

[a] An estimate of percentage formation comparing integration of the GC–MS trace of **3** to all other signals in the GC–MS chromatogram.

The effect of different acid catalysts, as well as amounts of acid, on the aldol reaction between benzaldehyde and MEK was investigated, with the results being summarised in Table 2. The results varied from no product detected (acetic, trifluoroacetic and *p*-toluenesulphonic acids) to reasonable yield (sulphuric acid, 40%). The various forms and amounts of aqueous hydrochloric acid were not as effective as the dry gas originally used.

The second change made to the original reaction conditions was the stoichiometry of MEK used in the reaction. As seen in Fig. 2, the most significant by-product formed in the aldol reaction is **9**, which is presumably produced from a second aldol condensation reaction between **3** and benzaldehyde. It was found that when more equivalents of MEK were used in the reaction less of **9** was formed. Shown in Fig. 8 is a graph of the approximate sum of **9** and **10** formed (as determined by GC–MS) when different amounts of MEK were used in the reaction. When half an equivalent of MEK was used, 40% of the crude product was **9** and **10** under the reaction conditions where **9** would be expected to form.

The percentage by-product formed is estimated from the integration of the GC–MS traces and gives an indication as to the significance of **9** and **10**. The number of equivalents of MEK recommended by "The Hive" method was just over two which, judging by our results in Fig. 8, should mean that 15–20% of material is **9** and **10**. From the above results it is clear that the

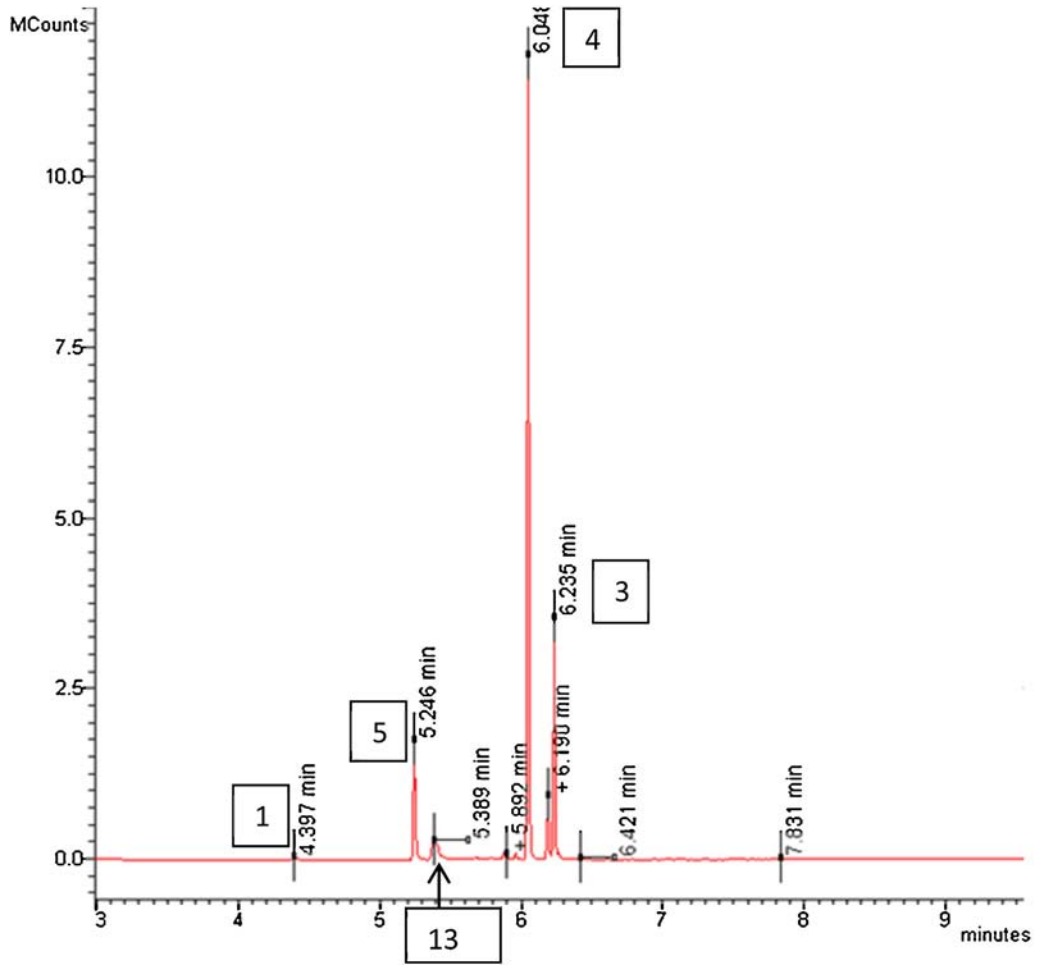


Fig. 10. Partial GC–MS trace of the Baeyer–Villiger reaction mixture after workup.

amount of MEK used in the reaction is quite crucial with insufficient MEK favouring the double aldol adduct **9**.[4]

3.4. Baeyer–Villiger reaction

The second step in the reaction pathway that bears their names is the actual Baeyer–Villiger reaction itself. The Baeyer–Villiger reaction is well known in traditional organic chemistry for the transformation of ketones into esters and cyclic ketones into lactones [6]. In this case the Baeyer–Villiger reaction is used to convert **3** into 2-acetoxy-1-phenyl-1-propene **4.** Thus **3** was allowed to react with peracetic acid, which is formed *in situ* when glacial acetic acid is treated with sodium perborate. Sodium perborate is an unusual reagent for a Baeyer–Villiger reaction but not unheard of [7,8].

Fig. 9 shows a scheme of the Baeyer–Villiger reaction of **3** to yield ester **4** and subsequent hydrolysis of the ester to form P2P **5**. Under the reaction conditions some ester **4** is hydrolysed to P2P, which is then able to react further under the Baeyer–Villiger conditions to produce **13** and **14**. Shown in Fig. 10 (with compound structures collected in Table 3) is a GC–MS trace of the reaction after workup and extraction of the organic components with the major product from the reaction being the desired ester **4**. **4** is reported in the literature as a by-product formed from the manufacture of P2P from phenylacetic acid using acetic anhydride. It is commonly referred to as the 'acetate of P2P' or the 'acetate enol of P2P' and is formed under these condition when the enol of P2P attacks acetic anhydride [3]. In addition, there are large amounts of both *cis-* and *trans-* isomers formed [2]. However when **4** is produced in the Baeyer–Villiger pathway the *trans-* isomer is the major isomer with only traces amount of *cis-* isomer being formed due to the previous aldol reaction.

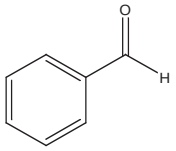
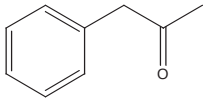
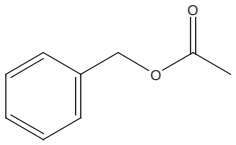
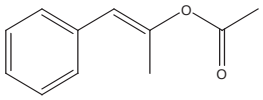
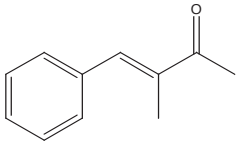
Having formed ester **4** in good yields the next step is a hydrolysis reaction to form P2P **5**. However some of the ester produced is hydrolysed during the Baeyer–Villiger reaction yielding P2P which is then able to undergo a second Baeyer–Villiger reaction to form benzyl acetate **13**. Subsequent hydrolysis of **13** yields benzyl alcohol **14**. Benzyl acetate is reported in literature as a by-product formed from the manufacture of P2P from phenylacetic acid using acetic anhydride [3].

The major product from the Baeyer–Villiger reaction is the desired ester **4** and the major product in the hydrolysis reaction is P2P, with typical yields of P2P over two steps being around 80% from **3**.

If the aldol product **3** had not been purified but used impure in subsequent steps, which most likely would be the case in clandestine laboratories, how would have the impurities identified be influenced by the Baeyer–Villiger reaction? Since we had independently synthesised these compounds we were able to answer this question directly. The Baeyer–Villiger reaction was

[4] "The Hive" method distilled **3**, which is a very effective and easy method of purification due to the large difference in boiling points of the major by-products. **3** has a boiling point of around 270 °C at atmospheric pressure which may make it hard for drug cooks to purify without scientific glassware and a vacuum pump.

Table 3
Chemical structure and compound numbers used in Fig. 10.

Compound number	Compound	Chemical formula	Mass spectrum data
1	 Benzaldehyde	Chemical formula: C_7H_6O Exact mass: 106.64	51 (10%), 77(25%), 105(base peak)
5	 Phenyl-2-propanone	Chemical formula: $C_9H_{10}O$ Exact mass: 134.07	43 (25%), 65 (15%), 91 (30%), 135 (base peak)
13	 Benzyl acetate	Chemical formula: $C_9H_{10}O_2$ Exact mass: 150.07	43 (30%), 65 (20%), 79 (40%), 91 (60%), 107 (base peak), 149 (10%)
4	 2-Acetoxy-1-phenyl-1-propene	Chemical formula: $C_{11}H_{12}O_2$ Exact mass: 176.08	43 (15%), 91 (20%), 133 (base peak), 176 (10%).
3	 3-Methyl-4-phenyl-3-buten-2-one	Chemical formula: $C_{11}H_{12}O$ Exact mass: 160.09	43 (15%), 63 (5%) 91 (7.5%), 115 (55%), 145 (10%), 159 (base peak)

found to be unsuccessful on the by-products (**8**, **9**) from the aldol reaction even at higher temperatures (100 °C) with starting materials being isolated after treatment with glacial acetic acid/sodium perborate. Conjugated systems are known to be less reactive under Baeyer–Villiger reaction conditions [9] which is presumably why **9** does not react since it contains extended conjugation. However **3** and **8** are both conjugated systems yet **3** reacted and **8** did not. This may be due to the lower migratory aptitude of the secondary group in **8** compared to the tertiary group in **3** [6]. The significance of sodium perborate in clandestine chemistry is that it allows the straightforward synthesis of peracids. Sodium perborate was sold as a laundry aid (*SARD Oxy Plus* (Colgate-Palmolive)) in the concentration range 10–30% [10]. The ease of access to sodium perborate is why our investigations have focused on *in-situ* formation of peracid over pre-formed peracid. *SARD Oxy Plus* has been shown to work in the Baeyer–Villiger reaction but resulted in a low crude yield of P2P [4]. Currently *SARD Oxy Plus* no longer contains sodium perborate, but instead uses sodium percarbonate in the concentration range 10-30% [11,12]. Household sodium percarbonate has been used in a Baeyer–Villiger reaction on cylcopentanone [13]. Sodium percarbonate is a source of dry hydrogen peroxide, with hydrogen peroxide able to be used in the Baeyer–Villiger reaction instead of peracids. Laboratory grade hydrogen peroxide (50% solution) was used in a Baeyer–Villiger reaction on **3** resulting in a crude yield of **4** of 94%[†] yet there were still some starting materials and trace amounts of P2P detected by GCMS. When sodium perborate is used in the Baeyer–Villiger reaction the sodium perborate reacts with acetic acid to form peracetic acid which is the reagent for the Baeyer–Villiger reaction [7].

A Baeyer–Villiger reaction using *SARD Oxy Plus* (containing sodium percarbonate) was performed on **3** under similar reaction conditions to that used for sodium perborate however only

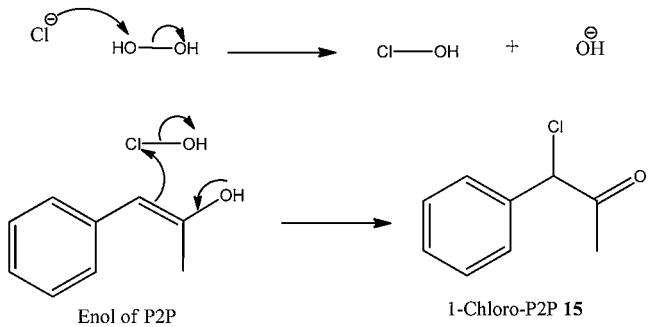


Fig. 11. Suggested mechanism for the formation of 1-chloro-P2P.

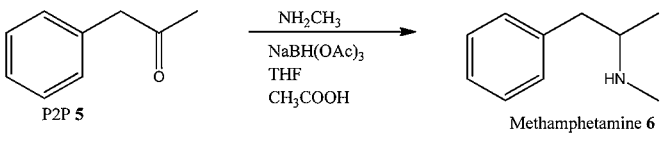


Fig. 12. Reductive amination reaction of P2P to methamphetamine.

unreacted **3** was isolated. However, a change in reaction conditions to only use acetic acid as the solvent in the reaction (ie no acetone) gave the ester **4** in 43% yield as determined by ^{1}H NMR‡. This reaction was incomplete, less P2P was detected by NMR and there was also a new impurity formed, which was identified as 1-chloro-1-phenyl-2-propanone (1-chloro-P2P) **15** in 21% yield from ^{1}H NMR‡. We have suggested a mechanism for the formation of 1-chloro-P2P (Fig. 11), where the enol form of P2P attacks a positive chloride ion in solution. The positive chloride could be formed *in situ* from chloride ion from sodium chloride reacting with hydrogen peroxide. 1-Chloro-P2P has been seen in clandestine seizures before and assumed it was a by-product in the reduction of ephedrine [14].

The third and final step in the Baeyer–Villiger route to amphetamine synthesis involves the reductive amination of the P2P **5** produced after ester hydrolysis of **4**. Such reductive amination reactions have been observed in clandestine laboratories employing a variety of reducing agents including Hg/Al, $NaBH_4$, and catalytic hydrogenation [1]. We have previously reported the use of sodium triacethoxyborohydride ($NaBH(OAc)_3$, STAB) for this reduction in yields of 85% (Fig. 12) [15]. STAB is common in mainstream organic chemistry but is an unusual reductive agent in clandestine chemistry and we have shown it to be very slow in the reduction of P2P to 1-phenyl-2-propanol. The reduction is so slow that no 1-phenyl-2-propanol is detected by GC–MS during the reductive amination of P2P to methamphetamine.

As conjugated systems are less reactive under Baeyer–Villiger reaction conditions it is not uncommon to see unreacted **3** after workup of the Baeyer–Villiger reaction. Thus, compounds such as **3**, **8**, and **9** could all be in the mixture when P2P **5** is treated using reductive amination conditions. All of these compounds have a keto functionality and so would be expected to also undergo a reductive amination reaction. However there is a competing reaction of conjugate addition due to the presence of the pi bond. In contrast, P2P does not have this pi bond so it is effectively converted to methamphetamine.

To investigate the compounds that would be produced by having either **3**, **8**, or **9** in the reaction mixture these materials were investigated in reductive aminations directly. When **3** undergoes a reductive amination reaction using the previously described conditions the major product was determined using GC–MS and NMR spectroscopy to be 2-(methylamino)-3-methyl-4-phenyl-3-butene **16** (Fig. 13). A similar impurity to **16** has been seen in methylamphetamine containing samples but without the conjugated pi bond [16]. However reduction of the double bond is possible (*vide infra*).

As STAB is an unusual reducing agent in clandestine laboratories several of the more commonly encountered clandestine reducing reactions were investigated. The first of these was sodium borohydride and in this case the major product of the reaction was 2-hydroxy-3-methyl-4-phenyl-3-butene **18** formed by the reduction of the ketone to the alcohol (Fig. 14), with **16** only present as the minor product.

The second alternative reductive amination reaction investigated involved hydrogen as the reducing species. Using $Pd(OH)_2/C$ as a catalyst, reaction with **3** yielded 3-methyl-4-phenylbutan-2-one **17** and 2-(methylamino)-3-methyl-4-phenylbutane **19** (Fig. 15). Under these conditions both the pi bond and the carbonyl are reduced indicating that the compound **17** detected previously [16] could have been produced by such reaction conditions.

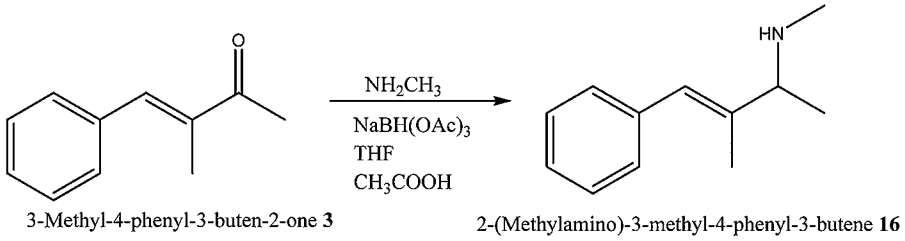


Fig. 13. Reductive amination reaction of compound **3** with STAB.

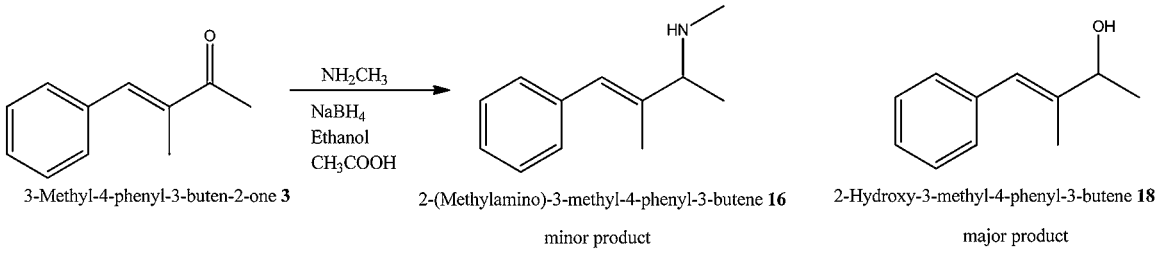


Fig. 14. Reductive amination of compound **3** with $NaBH_4$.

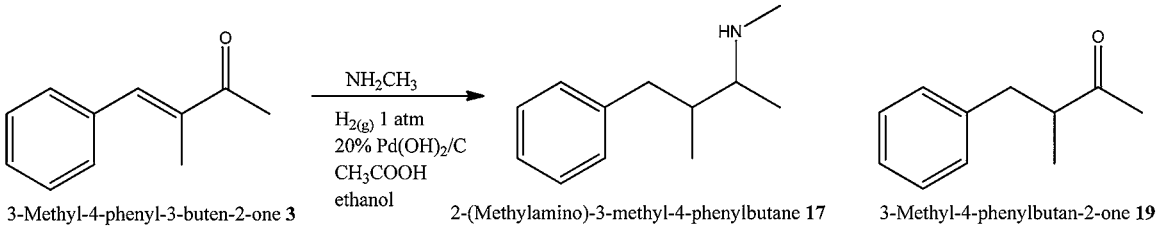


Fig. 15. Hydrogenation reaction of compound **3**.

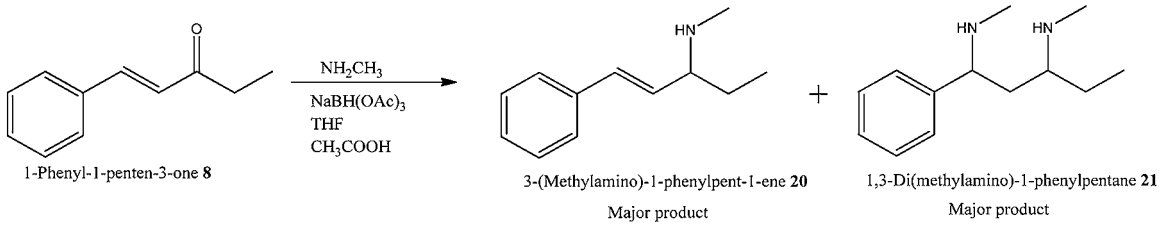


Fig. 16. Products formed in the reductive amination of compound **8**.

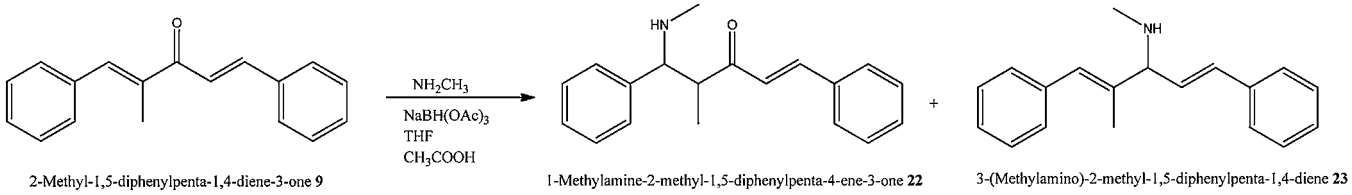


Fig. 17. Reductive amination reaction of compound **9**.

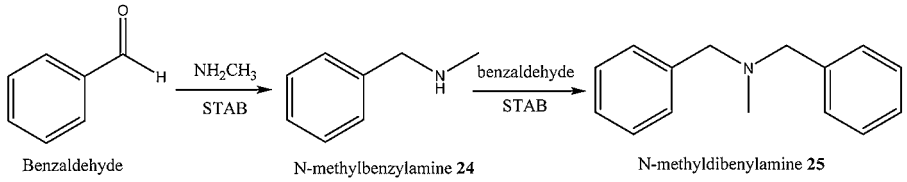


Fig. 18. Various products formed from the reductive amination of benzaldehyde with methylamine and STAB.

The next impurity to be subjected to the reductive amination reaction was the aldol regioisomer **8**. Under the conditions employed (STAB) the reaction yielded two major products. The first of these is the expected reductive amination product **20**, while the second product is when both reductive amination and conjugate additions reactions have occurred **21** (Fig. 16). It would be expected that **8** undergoes a conjugate addition first followed by imine formation and finally reduction to form **21**.

Finally we investigated the "double aldol" adduct **9** in a reductive amination reaction. Utilising methylamine/STAB conditions the major product was the mono addition product 1-(methylamino)-2-methyl-1,5-diphenylpenta-4-ene-3-one **22** (Fig. 17). 3-(Methylamino)-2-methyl-1,5-diphenylpenta-1,4-diene **23** formed by a reductive amination was also detected by GCMS. The identity of **22** was confirmed using both GC–MS and ^{1}H NMR and it is unclear why the addition reaction is so regioselective. Regioselectivity in conjugate additions is considered substrate or condition-dependent and is difficult to predict [17] and recently regio- and stereo- selective control have been imparted by the use of catalysts [18,19].

In many of the reductive amination reactions undertaken above the starting material contained trace amounts of benzaldehyde which reacted under the conditions to form N-methylbenzylamine **24** and which was seen in the GC–MS traces of reaction mixtures. Thus a reductive amination reaction was performed on pure benzaldehyde and the major product observed was N-methyldibenzylamine **25** and the minor product was N-methylbenzylamine **24** (Fig. 18). N-Methylbenzylamine **24** has been reported in the literature as a by-product from pseudoephedrine production from benzaldehyde and N-methylalanine [20].

4. Conclusions

We have investigated the impurities formed in the so-called Baeyer–Villiger pathway which describes the synthesis of P2P in a 60% yield from benzaldehyde in three steps; an aldol condensation of benzaldehyde and MEK; a Baeyer–Villiger reaction and subsequent ester hydrolysis. The majority of these impurities have been independently synthesised and characterised and may serve as route specific markers for the pathway. In particular these impurities are the aldol-derived adducts 3-methyl-4-phenyl-3-buten-2-one **3** and 2-methyl-1,5-diphenylpenta-1,4-diene-3-one **9**, as well as their reductive amination products 2-(methylamino)-3-methyl-4-phenyl-3-butene **16,** 3-methyl-4-phenylbutan-2-one **17** and 1-(methylamino)-2-methyl-1,5-diphenylpenta-4-ene-3-one **22**. We have also observed that some of the impurities formed in the initial steps of the Baeyer–Villiger pathway are unreactive in subsequent steps and are thus carried through to the final product.

Current investigations are centred on using different benzaldehydes substituted with various functional groups that alter the electronic properties of the aldehyde moiety in the Baeyer–Villiger pathway. For example, one of the most interesting aldehydes for clandestine chemistry is piperonal as it leads directly to the synthesis of MDMA (ecstasy).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.forsciint.2016.03.034.

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