

THE WILLGERODT-KINDLER REACTION. PART 1: STYRENE TO METHAMPHETAMINE

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ABSTRACT

The manufacture of methamphetamine by well-concealed means came to light after an explosion within a clandestine drug laboratory. Investigations disclosed that styrene was being used as the principal feedstock for the production of phenylacetic acid. This paper describes the process used and the implications it has for the illicit manufacture of amphetamines generally.



Photo 1: Damage caused to the laboratory area of the residence.



Photo 2: A gas cylinder embedded in the wall of an adjoining room viewed from the laboratory area.



Photo 3: Penetration of cylinder fragment through a second internal wall.

INTRODUCTION

Pseudoephedrine has been the mainstay of illicit methamphetamine manufacture in Australia for over a decade. However, restrictions placed on the sale and supply of key reagents, including pseudoephedrine, has led to an increase in alternative methods of drug production. An explosion at a residence in a southern suburb of Adelaide, South Australia, in December 2007 brought one such method to our attention.

The laboratory was producing phenylacetic acid from styrene using ammonia solution and elemental sulfur in a process known as the Willgerodt reaction. This process requires temperatures well above the boiling point of most of the reagents requiring the use of a pressure vessel. At the time of the explosion, a propane gas cylinder was being used as the pressure vessel for the reaction and a domestic electric oven was being used as the heat source (Photographs 1 – 3).

The phenylacetic acid produced in this manner was then converted to phenyl-2-propanone (P2P) by dry distillation from lead acetate. P2P was then converted to methamphetamine by methylamine/aluminium/mercuric chloride reductive amination. The methylamine was prepared from ammonium chloride and formaldehyde and *d*-tartaric acid was used to resolve the *d*- and *l*-enantiomers of methamphetamine. The chemicals required were all inexpensive and, with the exception of mercuric chloride, were not subject to scrutiny or reporting requirements. For the cost of a kilogram of 'black market' pseudoephedrine, over 4 tonnes of styrene could be purchased for conversion to approximately one tonne of methamphetamine. Factors weighing heavily against the use of this method include the perceived need for pressure vessels and the stench of sulfides produced during the reaction; however, both factors can be overcome.

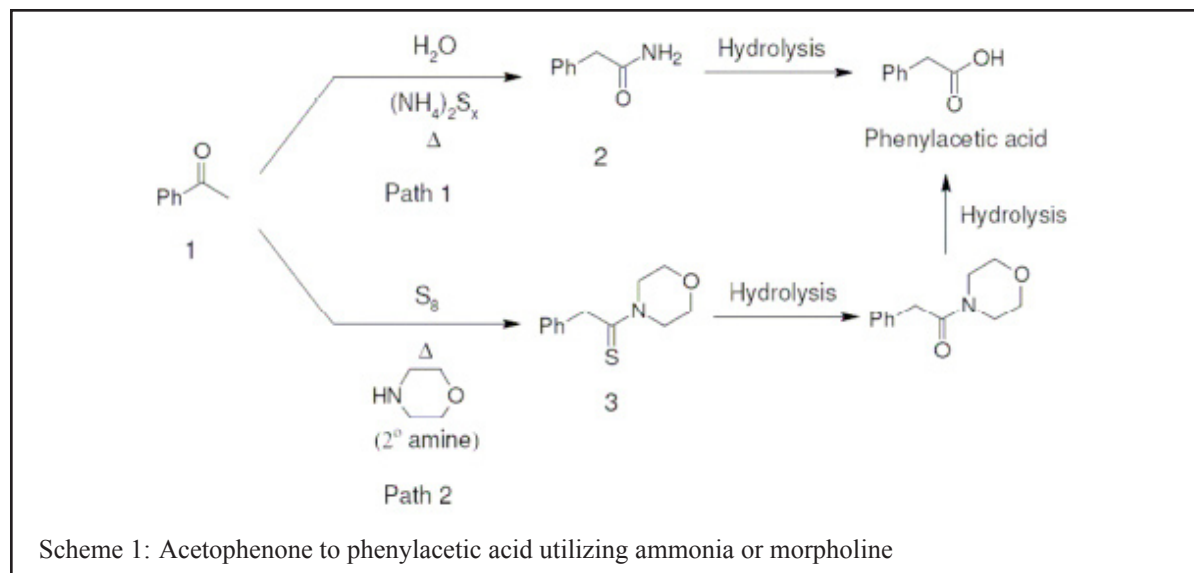
STYRENE AS A PRECURSOR TO PHENYLACETIC ACID: HISTORY AND CHEMISTRY OF THE WILLGERODT REACTION.

The reaction was originally performed on acetophenone (1) by Conrad Willgerodt [1] to produce phenylacetamide (2) as shown in Scheme 1, Path 1.

A modification introduced by Kindler [2] replaced ammonia with amines and the thioamide produced could be readily hydrolysed to the amide. Morpholine was found to be a particularly effective reagent and solvent [2] (Scheme 1, Path 2) to produce phenylacetothiomorpholide (3) and its hydrolysis product, phenylacetic acid. Tertiary amines did not promote the reaction [3].

Carmack [4] observed that the position of the carbonyl group was not crucial, and that propiophenone (4) and phenylacetone (5) gave the same terminal amide (6) (Scheme 2). It was discovered that compounds such as styrene, phenylacetylene and 1-phenylethanol also produced 2 under the Willgerodt conditions [5-7] (Scheme 3).

Further investigations into the reaction mechanism revealed that internal alkenes and alkynes [6] and aliphatic and alicyclic ketones all produced terminal amides under the Willgerodt conditions and that the efficiency of the conversion diminished with increasing chain length [4, 5] (Scheme 4). It was also established that unactivated alcohols required more forcing conditions since their dehydration to alkenes was the key initial step in the conversion [8] (Scheme 5). King and McMillan showed that the carbon skeleton remained intact throughout the Willgerodt



reaction and that terminal carbon-hydrogen bonds were not involved in the initial reaction [9]. This was later confirmed using the isotopically labelled substrate 1-[4-(methylthio)phenyl]ethanone-1-¹⁴C [10]. Determination of the mechanism of the transformation has been complicated by the complexity of the ammonia/sulfur mixture, which offers an array of nucleophiles, electrophiles, oxidants (S_8) and reducing agents (H_2S_y) [11] (Scheme 6). Diaminopolysulfanes ($x > 2$) can be used in place of the ammonia and sulfur mixture.

While the mechanism of the reaction is not fully understood, progress of the functionality to the terminus is likely to be the result of a series of addition and elimination steps. One representation of this process is illustrated in Scheme 7. More mechanistic detail can be found in reports by Purrello [11] and Carmack [12, 13].

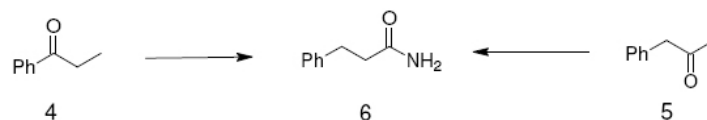
INVESTIGATIONS

Samples taken from the cylinder fragments and walls contained a mixture of predominantly phenylacetamide (2), benzamide and sulfur (Figure 1). Replication of the conversion, as described in notes found at the scene, but using a Teflon-lined bomb, produced a similar amide mixture (Figure 2 (upper trace)). The production of diphenylthiophenes has been noted previously [12], but the formation of 3,4-diphenyl-2,5-diazathiophene as indicated in the chromatogram is only speculative and is based on mass spectral data. Other notes indicated that the conversion had previously been conducted at 160°C and our replication of the process under those conditions improved the yield of phenylacetamide as oxidative cleavage of the side chain and heterocycle formation were significantly reduced (Figure 2 (lower trace)). We determined that the reaction did not proceed appreciably at 100°C, was incomplete after 10 hours at 130°C and gave optimal conversion at about 160°C. While the optimum temperature still requires the use of a sealed system, the pressures developed would be much less than those generated at 200°C.

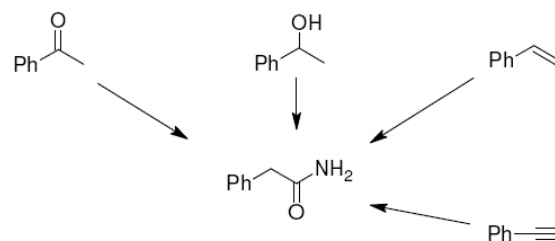
THE KINDLER MODIFICATION

Morpholine was located within the laboratory and its use, as both reagent and solvent in place of ammonia solution and ethanol, leads to the formation of phenylacetothiomorpholine (3) (Figure 3 (upper trace)). For comparison purposes acetophenone was used in place of styrene and the product mix was found to be essentially unchanged and exhibited substantial amounts of cleavage product (Figure 3 (lower trace)).

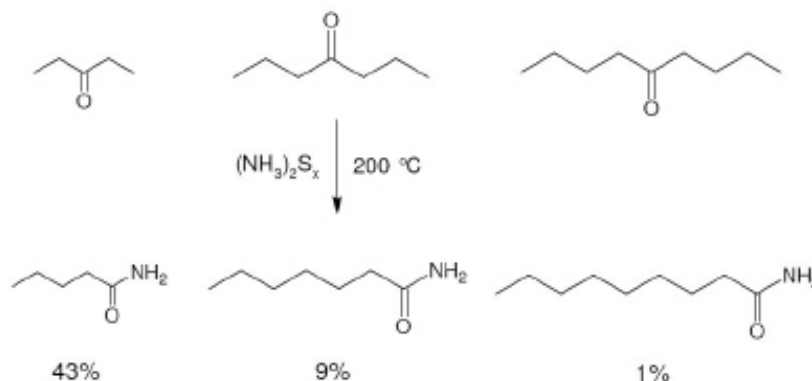
Reducing the reaction temperature to the mixture's atmospheric-pressure boiling point of about 130°C resulted in a very clean product within 30 minutes (Figure 4). Further



Scheme 2: The equivalence of carbonyl position



Scheme 3: A choice of precursors



Scheme 4: Terminal amide formation as a function of chain length



Scheme 5: More forcing conditions for an unactivated substrate

temperature reduction to 90°C resulted in a similar reaction mixture after 4.5 hours. Mild reaction conditions using sonication [14, 15] and phase-transfer catalysis [16] have also been reported and acid hydrolysis to phenylacetic acid is straightforward [17].

IMPLICATIONS FOR ILLICIT DRUG MANUFACTURE

A range of cheap, unrestricted chemicals, without the use of a pressure vessel, can be used as precursors to phenylacetic acid via the Willgerdt-Kindler modification, using morpholine. Unconstrained by the use of pressure vessels, this process becomes a realistic option for large-scale production of phenylacetic acid. In addition, substituted styrenes (Scheme 8; X = Cl, OH, NH₂; X ≠ NO₂) have been shown to produce the corresponding amides provided the substituent is not susceptible to reduction [17]. This raises the possibility of using the Willgerdt-Kindler method to produce many substituted amphetamines from readily available substrates. We are continuing investigations into such options in this laboratory.

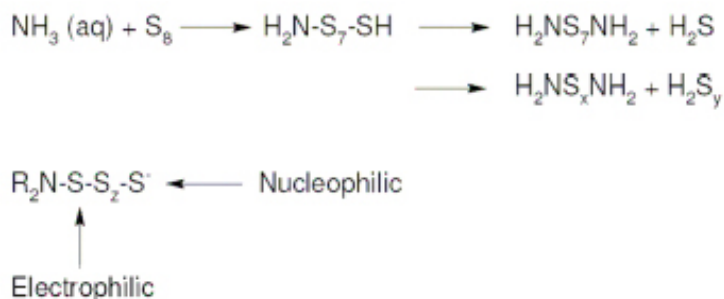
EXPERIMENTAL

Chemicals and reagents

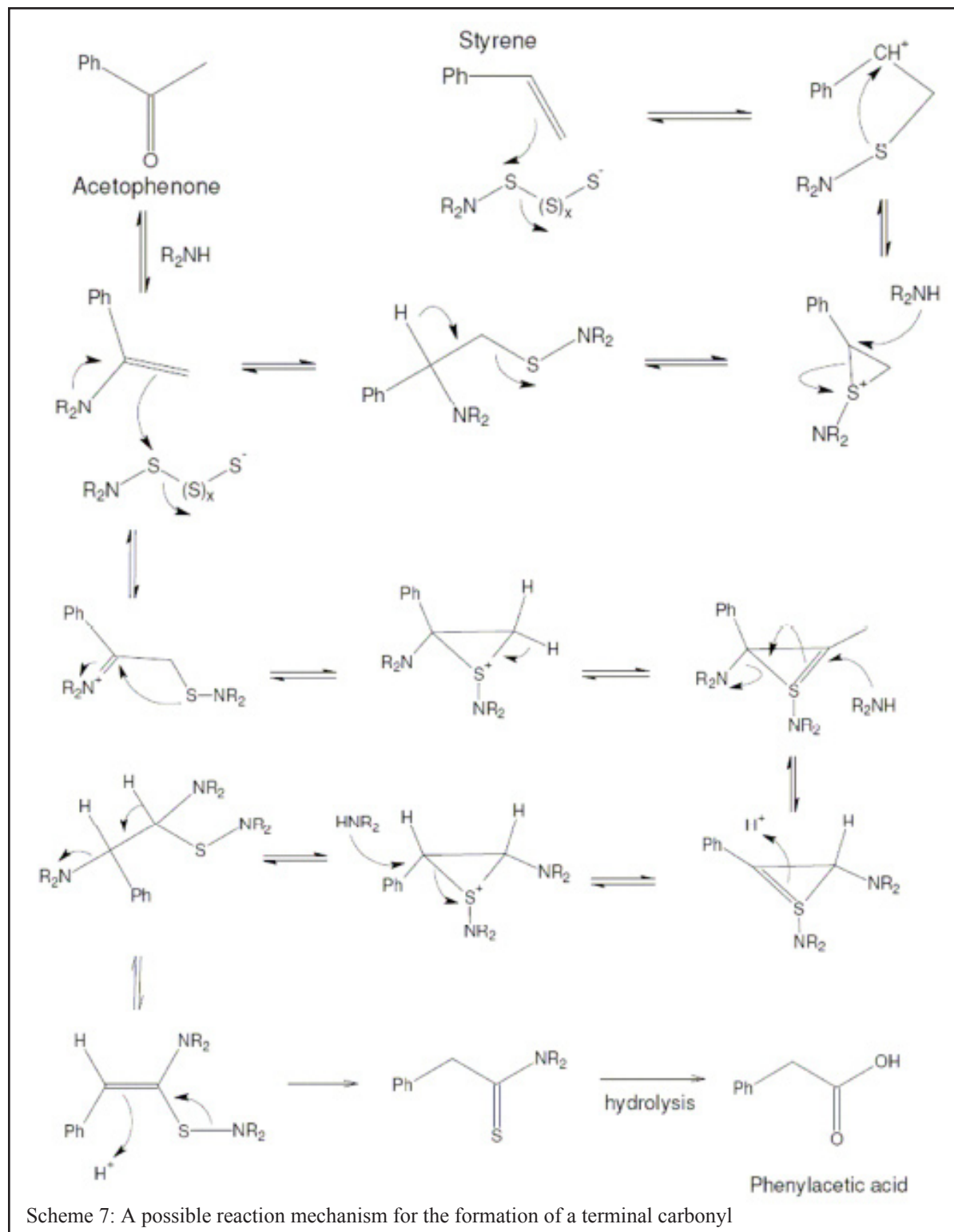
All solvents, acids and 30% ammonia solution used in this work were of analytical grade. Styrene (Reagent Plus >99%) and morpholine were purchased from *Aldrich* and *May and Baker* chemical companies respectively. Sulfur powder (99.9%) from *Manutec Pty. Ltd.* was acquired from a garden supply outlet.

Equipment and instrumentation

Closed reactions were performed in a *Parr Instruments* acid digestion bomb, model 4749 (45 mL capacity). The oven of a decommissioned *Hewlett-Packard* 5890A gas chromatograph was used to heat the bomb as it afforded good control over temperatures and heating times. Open



Scheme 6: The complexity of ammonia – sulfur mixtures



reactions were conducted in standard Pyrex flasks. Bleach proved useful for deodorising glassware and other implements prior to their removal from the fume cupboard. Sample analysis was effected with gas chromatography-mass spectrometry (GC/MS), viz. an Agilent 6890 Plus gas chromatograph with electronic pressure programming and a 5973 mass selective detector (MSD) operated from 40 to 450 amu in electron impact (EI) mode with an ionization energy of 70eV. Helium was used as a carrier gas at constant flow of 63 cm/s; the column was a 15 m

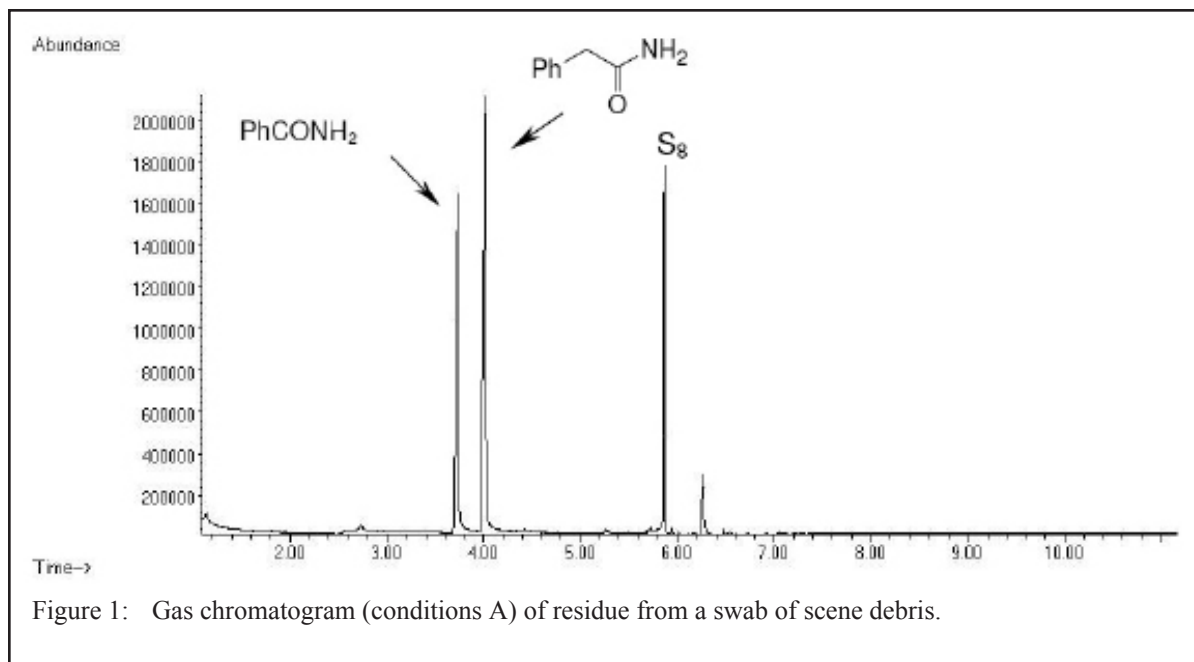


Figure 1: Gas chromatogram (conditions A) of residue from a swab of scene debris.

x 0.25mm x 0.25 μ m HP-1ms fused-silica capillary and the injection port was held at 300°C. Chromatographic conditions A: The initial column temperature was 90°C for 2.5 minutes and then ramped at 45°C/min to 300°C and a solvent delay of 1 minute was applied. Chromatographic conditions B: The initial column temperature was 40°C for 3 minutes and then ramped at 20°C/min to 200°C and a solvent delay of 1.50 minutes was applied. A *Thermo Scientific* Nicolet 6700 FTIR at 4cm⁻¹ resolution was used to collect the infrared spectrum.

General procedure for the synthesis of phenylacetamide (2) using a pressure vessel

The bomb was charged with sulfur (0.5 g), styrene (0.3 mL), ethanol (0.4 mL) and concentrated ammonia solution (0.5 mL), then sealed and placed in a pre-heated oven for the requisite time. The cooled mixture was acidified with dilute hydrochloric acid (to enable recovery of acidic hydrolysis products) and extracted with dichloromethane. The extract was washed with water and dried with sodium sulfate prior to analysis.

General procedure for the synthesis of phenylacetothiomorpholide (3) using a pressure vessel

The bomb was charged with sulfur (0.5 g), styrene (0.3 mL) and morpholine (0.6 mL) then sealed and placed in a pre-heated oven for the requisite time. The cooled mixture was acidified with dilute hydrochloric acid (to enable recovery of acidic hydrolysis products) and extracted with dichloromethane. The extract was washed with water and dried with sodium sulfate prior to analysis.

General procedure for the synthesis of phenylacetothiomorpholide (3) from styrene and morpholine at atmospheric pressure.

A mixture of styrene (5 mL, 0.043 mol), sulfur (3.49 g, 0.109 mol) and morpholine (7.57 mL, 0.087 mol) was stirred and heated at selected temperatures. Dichloromethane (CH₂Cl₂, 15 mL) and water (15 mL) were added to the cooled reaction mixture and the CH₂Cl₂ layer separated. The aqueous layer was then extracted with CH₂Cl₂ (2 x 15 mL). The combined CH₂Cl₂ extracts were washed with a solution of 10% HCl solution (50 mL) and then water (45 mL). The CH₂Cl₂ layer was dried over Na₂SO₄, filtered and evaporated. The crude product was recrystallized from hexane to afford 4.3 g (45%) of 3 as pale yellow needles (m.p. 74-76°C, lit 76-78°C [6]) in accord with a reported yield of 51% under similar conditions [6]. The mass and infrared spectra are provided in figures 5 and 6.

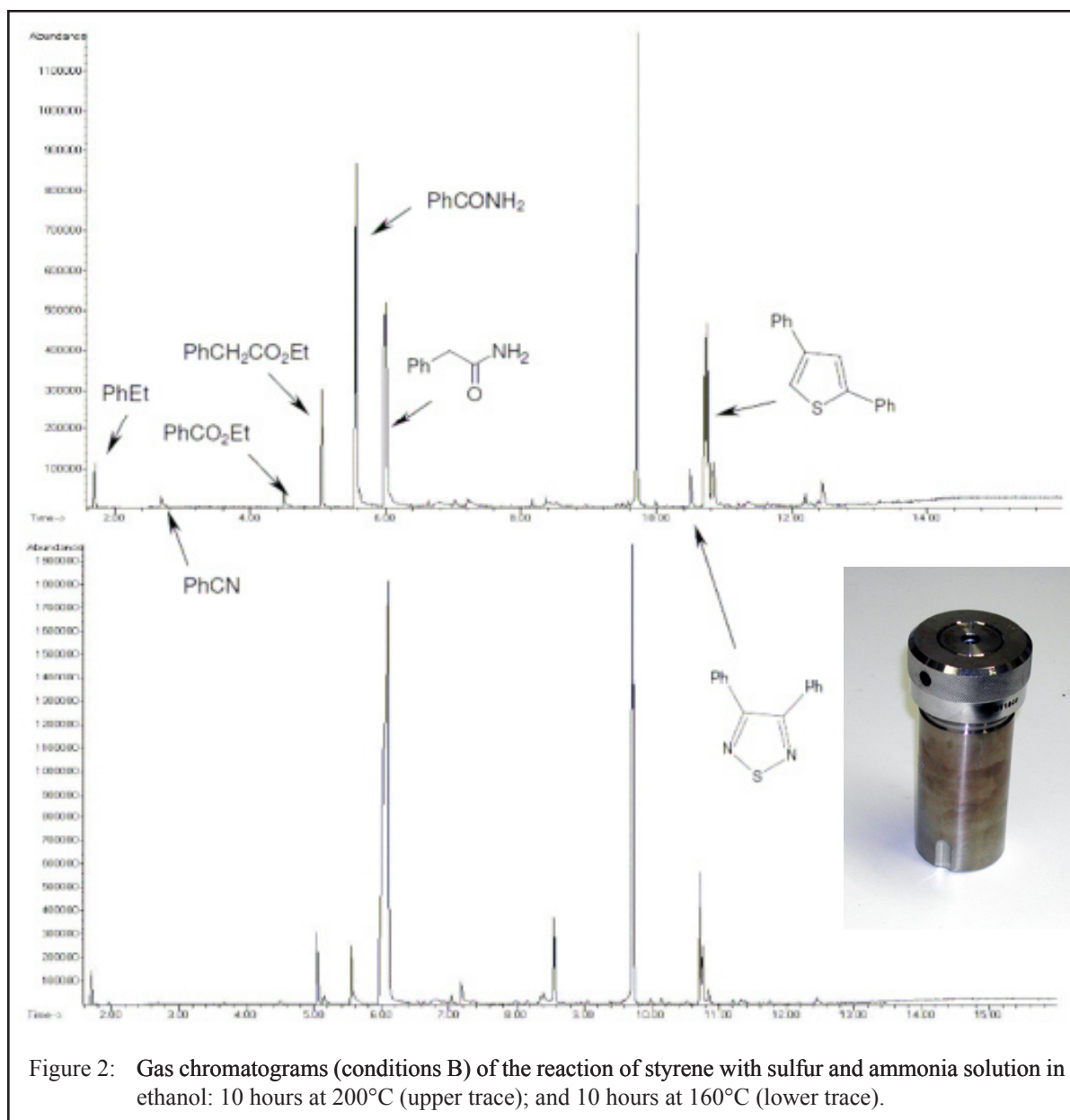


Figure 2: Gas chromatograms (conditions B) of the reaction of styrene with sulfur and ammonia solution in ethanol: 10 hours at 200°C (upper trace); and 10 hours at 160°C (lower trace).

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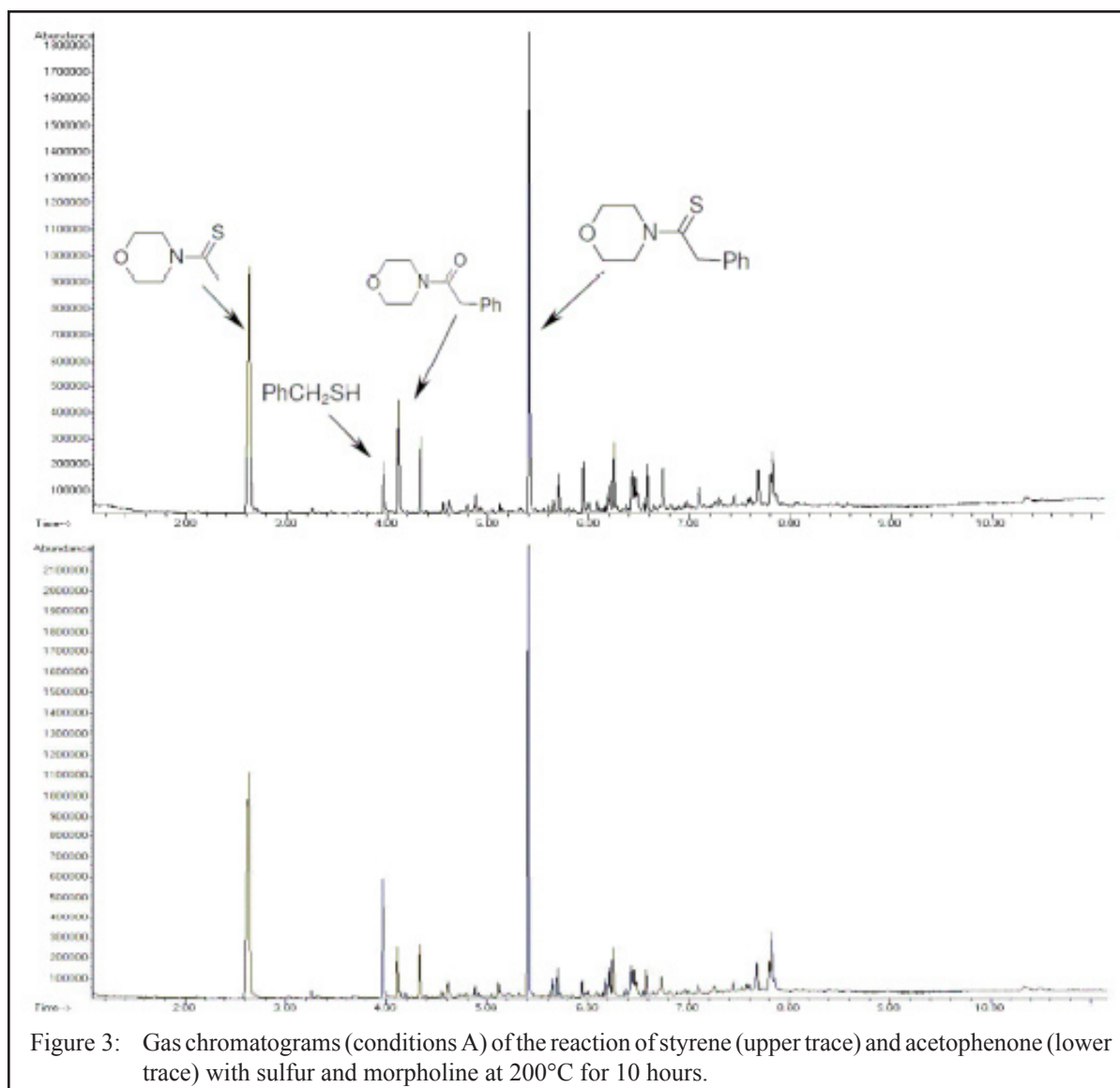


Figure 3: Gas chromatograms (conditions A) of the reaction of styrene (upper trace) and acetophenone (lower trace) with sulfur and morpholine at 200°C for 10 hours.

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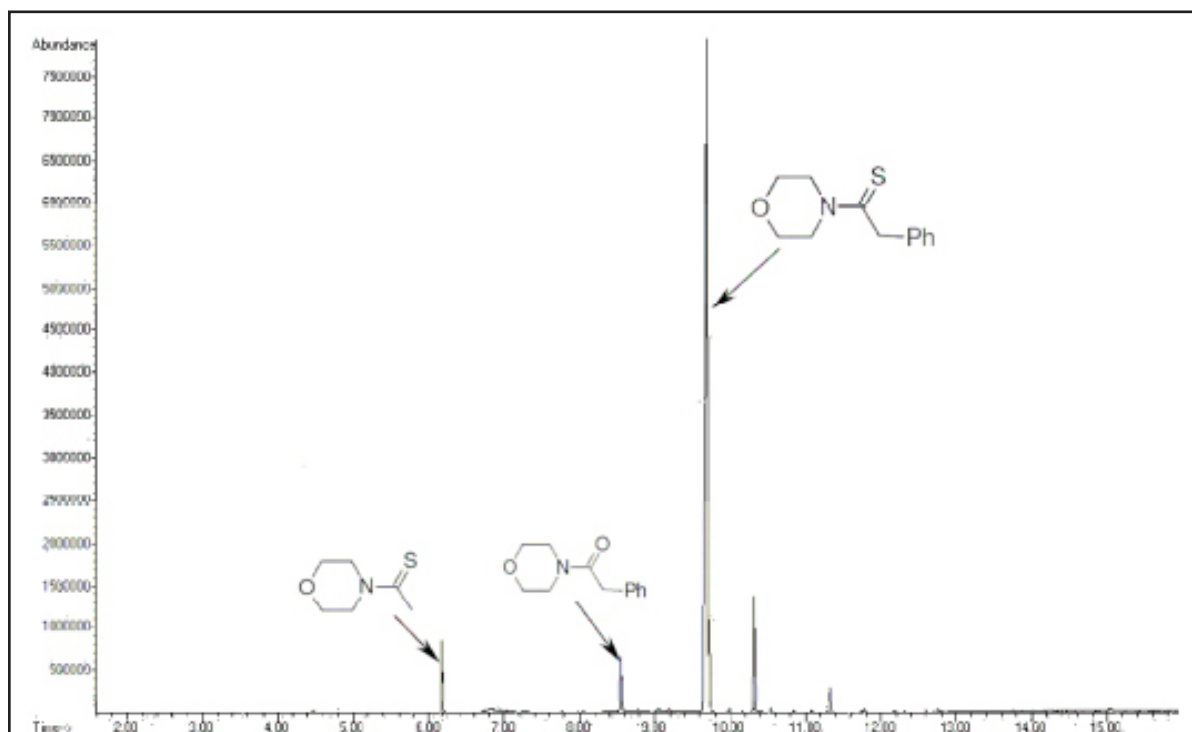
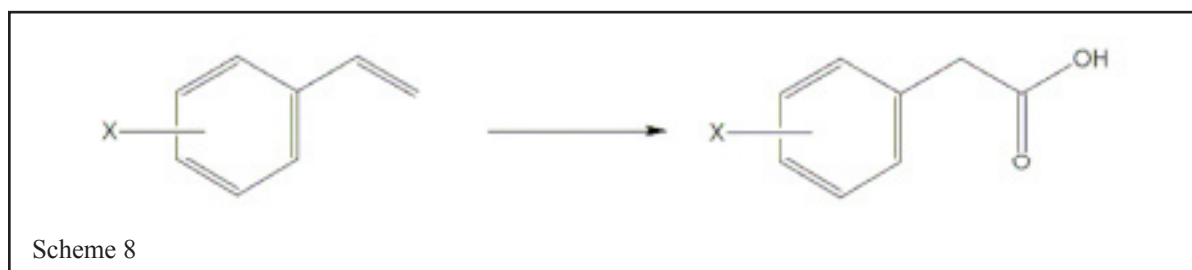


Figure 4: Gas chromatogram (conditions B) of the reaction of styrene with sulfur and morpholine under reflux at atmospheric pressure.



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