Anise Oil as a Precursor for 2-Alkoxy-5-methoxybenzaldehydes

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ABSTRACT: Anethole, the principal component of anise oil, is occasionally utilized as a precursor to anisaldehyde, which in turn is used as a precursor in the illicit synthesis of 4-methoxyamphetamine and 4-methoxymethamphetamine. Anethole can also be utilized as a precursor for 2,5-dimethoxybenzaldehyde and 2-ethoxy-5-methoxybenzaldehyde. 2,5-Dimethoxybenzaldehyde is a precursor for designer dimethoxyphenylethylamines that are subject to abuse, such as 2C-B, DOB and DOI, while 2-ethoxy-5-methoxybenzaldehyde can be similarly used to synthesize some of the so-called "Tweetios" (methylene insertion analogs of the corresponding dimethoxy compounds). In these synthetic routes, anethole is first oxidized to anisaldehyde, which in turn is converted to 4-methoxyphenol via a Baeyer-Villiger reaction. The phenol is formylated via a Reimer-Tiemann reaction, and the resulting benzaldehyde can be methylated to give 2,5-dimethoxybenzaldehyde, or ethylated to give 2-ethoxy-5-methoxybenzaldehyde. The described procedures are of forensic and judicial interest.

KEYWORDS: Anise Oil, Anethole, Anisaldehyde, 4-Methoxyphenol, 2,5-Dimethoxybenzaldehyde, 2-Ethoxy-5-methoxybenzaldehyde, Forensic Chemistry

Introduction

Anise oil is the common trade name for the essential oils of two different plant species, *Pimpinella anisum* and *Illicium verum*. Most commercially available anise oil is derived from *Illicium verum* (also known as star anise), and is grown primarily in the Far East. Anise oil from *Pimpinella anisum* has a sweeter taste and a more agreeable odor, and is usually grown in Central Asia and the Mediterranean region.

The main component of anise oil is anethole, 4-methoxyphenyl-1-propene [**1**]. Both varieties of anise oil contain 80 - 90 % anethole (1a,b). The essential oil derived from fennel (*Foeniculum vulgare*) also has a high anethole content, usually 50 - 60 %. Anethole is industrially utilized as a precursor for 4-methoxyphenyl-2-propanone, a valuable chemical stock. We recently demonstrated that anethole had been used as the precursor for clandestinely prepared 4-methoxyamphetamine (PMA) or 4-methoxymethamphetamine (PMMA) through 4-methoxyphenyl-2-propanone (2). This synthetic route is analogous to the syntheses of the methylenedioxyamphetamines (MDA, MDMA, or MDEA) from 3,4-methylenedioxyphenyl-2-propanone, prepared from isosafrole.

During our study of the preparation of 4-methoxyamphetamine starting from anethole, we noted that 4-methoxyphenol [**3**] was formed during the performic acid oxidation of anethole in the synthesis of 4-methoxyphenyl-2-propanone (2). It was determined that 4-methoxyphenol was formed by the Baeyer-Villiger oxidation of anisaldehyde (4-methoxybenzaldehyde [**2**]), which was present in the reaction mixture as an impurity originating from the peracid oxidation of anethole. 4-Methoxyphenol is recovered in an industrial process using a similar per-oxidation procedure (3). Therefore, we decided to explore whether 4-methoxyphenol could be formed from anethole as the primary product (that is, not as a side-product). If so, this would represent a possible route for the preparation of several 2,5-dimethoxyphenethylamines and 2-ethoxy-5-methoxy-phenethylamines (see Figure 1).

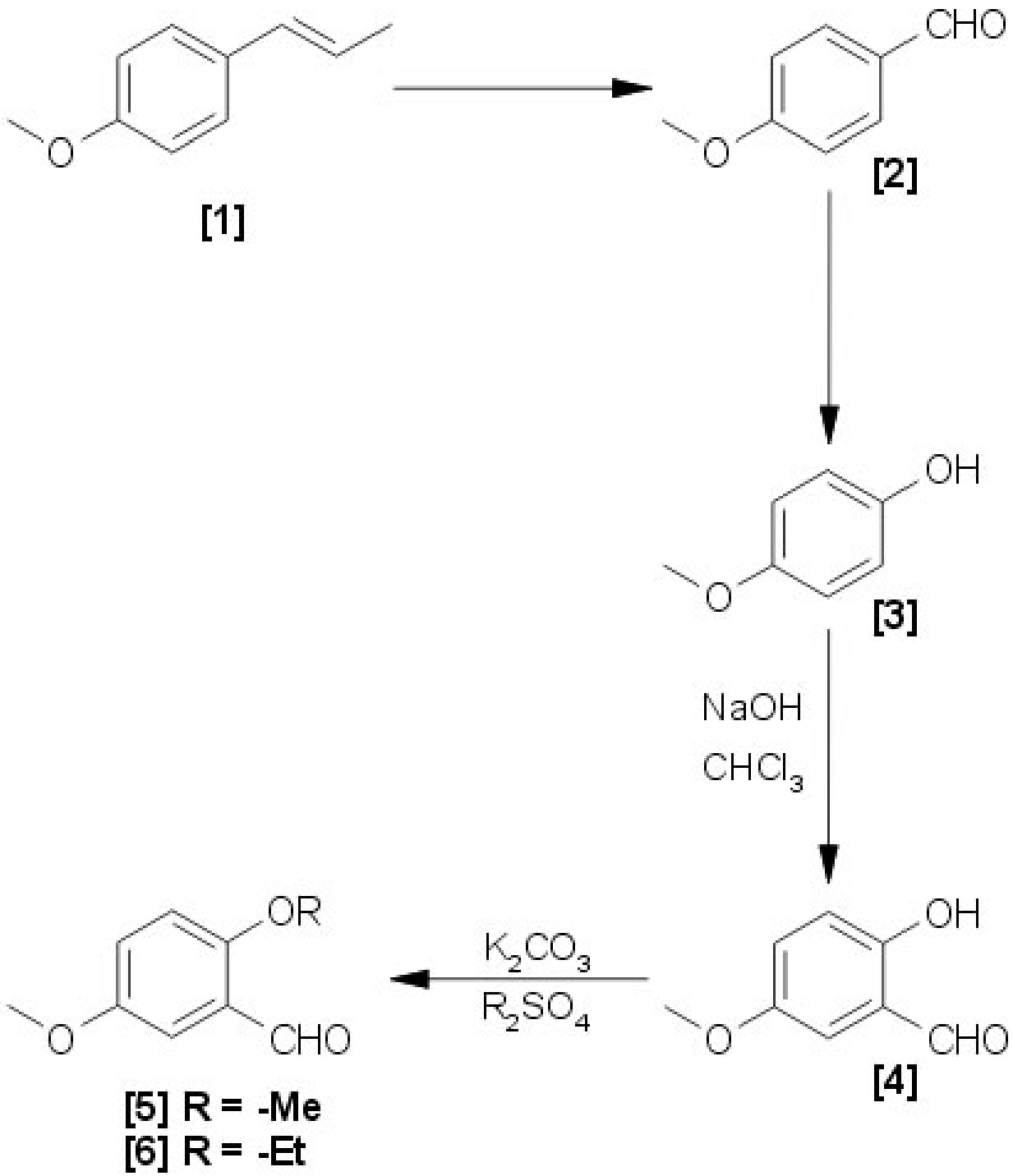

Figure 1: Anethole [**1**] is oxidized to anisaldehyde [**2**], which is subjected to a Baeyer-Villiger oxidation to give 4-methoxyphenol [**3**], which is subjected to a Reimer-Tiemann formylation to give 2-hydroxy-5-methoxybenzaldehyde [**4**]. Methylation gives 2,5-dimethoxybenzaldehyde [**5**], while ethylation gives 2-ethoxy-5-methoxybenzaldehyde [**6**]. Compounds **5** and **6** can be utilized as precursors for various 2,5-dimethoxylated phenethylamines or 2-ethoxylated-5-methoxylated phenethylamines. For details, see the Experimental Section.

Experimental

Chemicals and Reagents

All solvents used in this work were analytical grade and purchased from Acros Organics (Geel, Belgium). Anise oil was obtained from Taiga International NV (Breendonk-Puurs, Belgium), and originated from China (harvest year 2000) from *Illicium verum* (star anise). All other reagents were acquired from Merck (Darmstadt, Germany) or were synthesized from anethole (*vide infra*).

Instrumentation

Mass spectral analysis was performed on an Agilent 6890 Plus GC coupled to an Agilent 5973N MSD, and are presented in Figure 2. An HP-5-MS capillary column (30.0 m x 0.25 mm x 0.25 μm) was employed. Helium was the carrier gas, with a constant flow of 0.6 mL/min. The transfer line and ion source were operated at 280^{O} C and 230^{O} C, respectively. Mass spectra were recorded from 35 to 550 amu. The mass spectrometer was run in the Electron Impact (EI) mode with an ionization energy of 70 eV. A solvent delay of 4 min was applied. Oven temperature programming was as follows: 1 min at 50^{O} C, to 100^{O} C at 35^{O} C/min, to 270^{O} C at 10^{O} C/min. This temperature was maintained until the end of the programmed run (39.48 min). Injections were done split or splitless, depending on the nature of the sample.

Syntheses

Anisaldehyde (4-Methoxybenzaldehyde [**2**])

A freshly prepared and stirred solution of 30 mL concentrated sulfuric acid in 150 mL water was allowed to cool down to 30^{O} C, and anise oil (9.8 g) was added. A total of 25 g sodium bichromate was then added, at such a rate that the reaction temperature remained between 35 - 40^{O} C. The reaction mixture was extracted four times with toluene (75 mL each), and the combined organic phases were washed twice with 5 % NaOH (100 mL each), and once with water (100 mL). The organic phase was evaporated to about 20 mL, and anisaldehyde was then isolated as its bisulfite adduct. The yellow precipitate was washed with an EtOH/ether (1:1) mixture until the precipitate's color turned white (that is, similar to the bisulfite adduct generated from commercially available anisaldehyde). Setting the anisaldehyde free resulted in 4.9 g of a yellow oil with a pleasant odor. The mass spectrum was in agreement with an authentic sample. Anisaldehyde was the main product (95 % by GC/MS), but several minor impurities (not further identified in this report) were noted.

4-Methoxyphenol [**3**]

Performic acid was generated by mixing 23 g 30 % hydrogen peroxide with 19 mL 98 - 100 % formic acid and allowing it to react for 30 minutes. The resulting mixture was added to a stirred solution of 12 mL anisaldehyde in 200 mL dichloromethane, and refluxed for 24 h. The solvent was removed via rotavap, and the resulting residue was dissolved in a mixture of 200 mL NaOH (20 %) and 75 mL MeOH. This mixture was stirred for an additional hour, after which the MeOH was removed via vacuum distillation. The mixture was acidified with concentrated HCl to pH 1, and then extracted with dichloromethane (2 x 150 mL) . The combined extracts were dried over anhydrous Na_2SO_4, then evaporated via rotavap to give 10.0 g of a brownish oil which solidified upon standing. Further purification gave 4-methoxyphenol as a white crystalline product. The mass spectrum was in agreement with an authentic sample.

2-Hydroxy-5-methoxybenzaldehyde [**4**]

A 500 mL three-necked round bottom flask, equipped with reflux condenser, thermometer, and magnetic stirrer, was charged with 80 g NaOH and 100 mL water and stirred until dissolved. 30 g 4-methoxyphenol was then added to the still hot and stirring solution. Once the temperature dropped to 70^{O} C, 40 mL chloroform was added drop-wise over the course of 3.5 h, while the reaction temperature was maintained at 65 - 70^{O} C. During the reaction, yellow-green crystals formed on top of the mixture. When all of the chloroform was added, the reaction was continued for an additional hour, after which the mixture was acidified with chilled, 10 N H_2SO_4 to pH 2 - 3. A brown oil separated on top, and was isolated, and the residual aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was removed via rotavap. The resulting oil was added to the previously isolated oily layer and

steam-distilled. The distillate (2.5 L) was extracted with dichloromethane, and the organic layer isolated and washed with chilled water. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed via rotavap. The residual yellow oil (2-hydroxy-5-methoxybenzaldehyde) weighed 23.8 g and was used in subsequent reactions without further purification.

2,5-Dimethoxybenzaldehyde [**5**]
A 250 mL round-bottomed flask was equipped with a reflux condenser, thermometer, and magnetic stirrer, and was charged with 14 g anhydrous potassium carbonate, 10 g 2-hydroxy-5-methoxybenzaldehyde, and 100 mL acetone, and the mixture was brought to reflux. Once the mixture was boiling, 11 g of dimethyl sulfate was added, and the reaction was refluxed. After 3.5 h, the mixture was cooled, filtered, and the solvent was removed. The residue was taken up in 100 mL of cold water, and the precipitated crystals were collected and recrystallized from water/EtOH (1:1), giving (after drying in vacuo) 8.3 g 2,5-dimethoxybenzaldehyde as faintly yellow tinted needle-shaped crystals (GC purity: 98 %+). The mass spectrum was in agreement with an authentic sample. 1H-NMR δ 3.799 (s, 5-OMe), 3.893 (s, 2-OMe), 6.942 (d, J = 9.1 Hz, 1H), 7.135 (dd, J = 3.3 & 9.1 Hz, 1H), 7.326 (d, J = 3.3 Hz, 1H), 10.44 (s, 1H). 13C-NMR δ 55.69, 56.06, 110.45, 113.33, 123.41, 124.98, 153.63, 156.76, 189.60 (CHO).

2-Ethoxy-5-methoxybenzaldehyde [**6**]
A setup similar to the one described for 2,5-dimethoxybenzaldehyde was charged with 7 g anhydrous potassium carbonate, 7 g 2-hydroxy-5-methoxybenzaldehyde, and 100 mL acetone, and the mixture was brought to reflux. Once the mixture was boiling, 5 mL diethyl sulfate was added, and the reaction was refluxed. After 3 h, the mixture was cooled, filtered, and the solvent was removed. The residue was taken up into 75 mL of cold water, and the precipitated crystals were collected and recrystallized from water/EtOH (1:1), yielding spectacularly long, needle-shaped crystals. Recrystallization from EtOH gave 5.9 g 2-ethoxy-5-methoxybenzaldehyde as faintly yellow tinted, polymorphic crystals (GC purity: 98 %+). 1H-NMR δ 1.447 (t, J = 7.1 Hz, 3H), 3.794 (s, 3H), 4.106 (q, J = 7.0 Hz, 2H), 6.925 (d, J = 9.1 Hz, 1H), 7.111 (dd, J = 3.3 & 9.1Hz, 1H), 7.317 (d, J = 3.3 Hz, 1H), 10.473 (s, 1H). 13C-NMR δ 14.57, 55.63, 64.74, 110.08, 114.48, 123.47, 125.14, 153.54, 155.21, 189.72 (CHO).

Results and Discussion

The synthesis of anisaldehyde from anethole can be accomplished in several ways, for instance by reaction with ozone (4), VO_5 (5), or HNO_3 (6,7). We opted for the well-known sodium bichromate mediated oxidation. The applied procedure is a minor adaptation of a method used in the fragrance industry (6). The aldehyde was purified via its bisulfite adduct instead of distillation. Isolation as the bisulfite adduct is - in this case - a facile and low-priced alternative for purification via distillation. In fact, in the early 20th century, the bisulfite adduct of anisaldehyde was commonly traded as *aubépine cristallisée* for use in the perfume industry (*aubépine* translates from French as “hawthorn” (8)).

The synthesis of 4-methoxyphenol from anisaldehyde can be performed via the Baeyer-Villiger oxidation reaction with hydrogen peroxide or a peracid (9). We utilized performic acid in this study, but other peracids such as peracetic acid (10) or *meta*-chloroperbenzoic acid (11) work equally well. Other possibilities include sodium perborate in glacial acetic acid (12-14) or hydrogen peroxide with boric acid (15). Yields usually range between 70 % and quantitative, depending on which method was used.

The Reimer-Tiemann formylation reaction (16) is not widely utilized. Generally, low yields, several side-reactions, and easy formation of intractable tars are problematic. However, submission of 4-methoxyphenol to a Reimer-Tiemann formylation gives acceptable yields and reasonable workups. The scientific literature contains many references concerning adaptations for the Reimer-Tiemann formylation of 4-methoxyphenol, with yields usually varying between 40 - 70 %. In our study, we opted for a previously reported procedure by Wynberg and Meijer (17). Generally, this method has several advantages over the Vilsmeier-Haack formylation

(another widely used formylation technique, but which gives poor yields in this case). Even an improved version of the Vilsmeier-Haack reaction still gave only 40 % 2,5-dimethoxybenzaldehyde after 48 h of refluxing (18).

The methylation of phenols to methoxybenzenes using dimethylsulfate is well-known. The use of dimethylsulfate requires care due to its toxicity, but it may be substituted for by less toxic and easier accessible chemicals, such as dimethyl carbonate (19).

The synthesized benzaldehydes can be used for the preparation of several “designer” phenylethylamines; 2,5-dimethoxybenzaldehyde can be applied in the synthesis of, e.g.: 2C-B (20a), 2C-I (20b), DOB (20c), DOC (20d), DOI (20e), and 2,5-DMA (20f). Other phenylethylamines can be synthesized using 1,4-dimethoxybenzene, e.g.: 2C-P (20g). 2-Ethoxy-5-methoxybenzaldehyde is a precursor for the so-called "Tweetios" (20h). Tweetios are methylene insertion analogues of the 2,5-dimethoxyphenylethylamines, where one or both methoxy groups are replaced by ethoxy groups. These compounds generally display less potency and shorter duration time than the 2,5-dimethoxy analogues, and so do not have high potential for clandestine synthesis. In this case, only the 2-ethoxy-5-methoxyphenylethylamines can be obtained.

Anethole is currently used in large quantities in the alcoholic beverage industry (e.g., for Ouzo or Ricard), and in oral hygiene products (21). It is also a valuable component in aromatherapy products. Due to this economic significance, it is unlikely that anise oil or anethole will become monitored or scheduled substances, despite their use in the illicit production of PMA and PMMA, their link with several PMA- and PMMA-related fatalities over the past few years (2,22), and/or their potential use towards synthesis of various designer phenethylamines. We are currently unaware of any examples of anise oil or anethole being used to produce designer phenethylamines, but still feel it is necessary to point this possibility, since it might become a preferred precursor in the future as chemical substance controls are gradually increased. It is also important to understand that the presence of anise oil or anethole in a clandestine laboratory does not automatically imply that the operator intended to synthesize PMA and/or PMMA; it is also possible that synthesis of a designer phenethylamine was intended. This can only be ascertained by a total review of all chemicals and notes present at the laboratory, and/or by operator interviews.

Acknowledgements

We are grateful to Prof. Dr. Roger Busson (REGA Institute, K. U. Leuven) for recording of the NMR spectra reported in this study.

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[Note: Patents were retrieved via the Espacenet website http://gb.espacenet.com]

[Figure 2 Follows.]

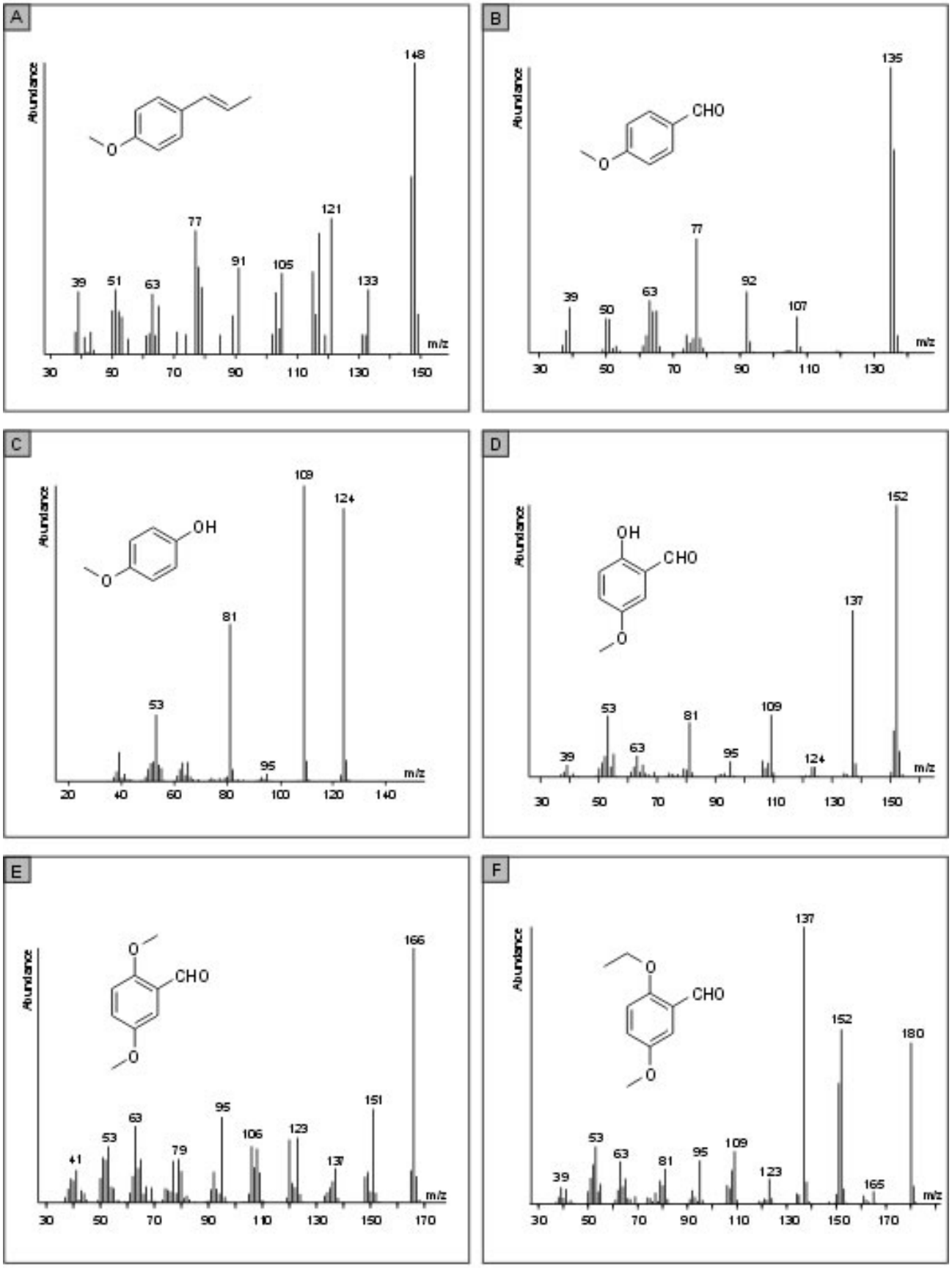

Figure 2: Mass Spectra of **1** - **6**.