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C. A. Valdez, R. N. Leif, B. R. Hart

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Carlos A. Valdez[1,2,*], *Roald N. Leif*[1,2] and *Bradley R. Hart*[1,2]

[1] *Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, Livermore, CA 94550, USA.*

[2] *Forensic Science Center, Lawrence Livermore National Laboratory, Livermore, CA 94550, USA.*

Corresponding Author:
Carlos A. Valdez, Ph. D.
Lawrence Livermore National Laboratory
7000 East Avenue, Livermore, CA, 94550, USA
Email: valdez11@llnl.gov
Phone: (925) 423-1804
Fax: (925) 423-9014

ABSTRACT

In the areas of chemical warfare agent (CWA) synthesis and degradation, *β*-amino alcohols are central species that can be used as indicators for the underlying presence of these lethal substances in a given matrix. To this end, we evaluated the derivatization of *β*-amino alcohols using phenyldimethylsilyl chloride (PDMSCl) in the presence of added nitrogenous bases for their detection and identification by EI-GC-MS. The three bases evaluated in this study were pyridine, *N*-methylimidazole (NMI) and 4-dimethylaminopyridine (DMAP) that due to their activation/acid scavenging abilities allows for the derivatization to be conveniently carried out at room temperature and under 30 minutes. In addition to common fragment ions originating from the phenyldimethylsilyl (PDMS) group, the derivatized *β*-amino alcohols yielded characteristic fragmentation patterns directly arising from their own structural make-up. Lastly, the retention times of the silylated alcohols were significantly increased relative to their parent alcohols, typical differences between these values were found to lie in the range of 6.7-9.1 minutes. The methodology presented herein describes a derivatization technique that is time-efficient and readily derivatizes the evaluated *β*-amino alcohols under mild conditions, characteristics that validate its use as an alternative approach to other commonly employed techniques compound analysis by EI GC-MS.

Keywords: silylation, pyridine, derivatization, amino alcohols, GC-MS.

Chemical derivatization to increase the volatility of analytes to make them suitable for GC-MS analysis is a commonly employed tactic in analytical chemistry. One of the most widely employed derivatization techniques is silylation where a tri-substituted silicon atom is directly appended onto the heteroatom of an amine, carboxylic acid or alcohol functionality [1]. Capping these hydrogen-bonding functional groups produces derivatives that exhibit higher volatility profiles and thus are more amenable for GC-MS analysis than their precursors [2-4]. Due to the wide impact in the field of GC-MS analysis produced by silylation, several reagents have been cleverly devised to carry out this derivatization. Unquestionably, some of the most widely used silylating reagents belong to the *N*-silyl-trifluoroacetylated amides, such as BSTFA (**1**) and MSTFA (**2**) (Figure 1) [5-8], that are employed to derivatize alcohols but can also modify carboxylic acids and amines [9, 10]. Even though these reagents have found widespread use, there remain certain aspects of their experimental manipulation that can be further improved upon. One such aspect is the introduction of the trimethylsilyl (TMS) functionality that in the full spectrum of silyl protective groups rank last in acid and basic stability [11]. In addition, the protocol for their use requires heating over several hours, usually to temperatures over 80 ^{o}C in order to obtain complete derivatization, making the approach problematic when encountering the analysis of temperature-sensitive substrates.

<Figure 1>

Alternate methods of silylation that do not involve the use of pre-activated silylating agent (*e.g.* BSTFA) exist and have found wide usage in the field of organic synthesis [12-15]. These methods involve the use of a silyl chloride in combination with an activating, nitrogenous base to

carry out the conversion of an alcohol into a silyl ether. The Corey group introduced the concept of *in situ* silyl chloride activation and in its original version, imidazole was the reagent of choice to smoothly and efficiently carry out the silylation of various alcohols [16]. The activation methodology has found a plethora of applications due to its ease of execution, its functional group tolerance, specifically in complex molecules, and the exceptionally mild conditions for its application [17]. Thus, the *in situ* silyl chloride activation strategy possesses several attractive features that make this alternate approach a suitable one for the derivatization of analytes for their subsequent detection by GC-MS techniques. Regarding the mild conditions for its execution, the reaction can be conveniently performed at ambient temperature, thus, avoiding the need for heating the analyte. Under these conditions the derivatization of alcohols is accomplished under 30 minutes. The short time required for the silylation to occur is of particular importance in laboratories where the fast identification of unknown analytes is critical.

Given the need for a reliable, mild and rapid derivatization for β-amino alcohols, we focused on the feasibility of employing the *in situ* activation protocol for the silylation reaction of this class of molecules. The nitrogenous bases evaluated in this study were pyridine, *N*-methylimidazole (NMI) and 4-dimethylaminopyridine (DMAP) (Scheme 1). Due to their structural features and electron density distribution on their nitrogen atoms, there are aspects of their reactivity that can be anticipated from their additions to the silyl chloride. In the case of pyridine, as it is commonly used as an acid scavenger, no acceleration on the overall rate of the silylation is expected. However, its presence remains beneficial to the reaction as it removes generated HCl from the reaction pathway (Scheme 1). In contrast, due to their enhanced nucleophilicity relative

to pyridine, NMI and DMAP are expected to react with phenyldimethylsilyl chloride to generate more reactive silylating species that can derivatize alcohols more efficiently (Scheme 1).

<Scheme 1>

With regards to the silyl group that is to be introduced in our panel of studied *β*-amino alcohols, we opted on employing the phenyldimethylsilyl (PDMS) protecting group for three reasons. The first one is based on the fact that after the derivatization, the resulting silyl ethers possess superior stability towards acid/base hydrolysis in contrast to their TMS counterparts. A second attribute is that in striking contrast to its trimethylsilyl (TMS) congener, the PDMS group is known to provide two signature fragmentation patterns such as loss of a methyl group ($[M-15]^+$) as well as protective group cleavage leading to the formation of the phenyldimethylsilyl cation (*m/z* = 135). These anticipated characteristic fragmentations would in principle aid in the unambiguous identification of a pool of analytes with similar structural features by providing additional, diagnostic fragments. Lastly, the success of PDMS installation in our analytes by this method strongly suggests that this approach will find success in the installation of less sterically demanding silyl groups such as TMS and triethylsilyl (TES), as well as other bulky groups such as the *tert*-butyldimethylsilyl (TBDMS).

As alluded to earlier, we have chosen to test this approach on a panel of *β*-amino alcohols, mainly for the presence of this motif in a myriad of interesting compounds such as neurotransmitters (epinephrine, **5**) [18] and stimulant drugs structurally related to ephedrine (**6**) [19] (Figure 2). However, it is its close association to compounds in the field of chemical

warfare agents (CWA) [20, 21] that serves as additional motivation for our lab to find alternative derivatization technologies for their identification as their detection in a given matrix may signal the underlying presence of one of these highly toxic substances [22-24] or provide critical chemical forensics information. For example, the *N,N*-substituted amino alcohols, where the substitution at the nitrogen consists of ethyl and isopropyl units represent hydrolysis products of organophosphorus-based nerve agents such as VX (**7**) and VR (**8**) respectively (Fig. 2). Additionally, *N*-substituted diethanolamines and triethanolamine are products directly arising from the hydrolysis of the nitrogen-based mustards (*e.g.* HN2 **9**, Fig. 2) [25, 26]. Lastly, the bicyclic *β*-amino alcohol 3-quinuclidinol, is a direct hydrolysis by-product of the incapacitating agent 3-quinuclidinyl benzilate (BZ, **10**) [27] (Fig. 2).

<Figure 2>

EXPERIMENTAL

Reagents and Chemicals

Anhydrous methylene chloride, *N*-methylimidazole (NMI), 4-dimethylaminopyridine (DMAP), phenyldimethylsilyl chloride, *N,N*-dimethylaminoethanol (**11**), *N,N*-diethylaminoethanol (**12**), *N,N*-diisopropylaminoethanol (**13**), *N*-methyldiethanolamine (**17**), *N*-ethyldiethanolamine (**18**) triethanolamine (**19**), *N*-propyl-2-aminoethanol, *N*-ethyl-2-aminoethanol, isobutyraldehyde, acetone, methanolic ammonia (NH_3/MeOH), and deuteriochloroform ($CDCl_3$) were purchased from Aldrich chemicals (St. Louis, MO.). *N,N*-dipropylaminoethanol (**14**), *N*-propyl-*N*-isopropylaminoethanol (**15**), and *N*-ethyl-*N*-isobutylaminoethanol (**16**) were synthesized as described below. 3-Quinuclidinol (**20**) and silica gel were purchased from Alfa Aesar (Ward Hill, MA.). Solvents used during the syntheses were removed by using a Büchi rotary evaporator R-200 equipped with a Büchi heating bath B-490 and coupled to a KNF Laboport Neuberger UN820 vacuum pump. Analytical thin layer chromatography (TLC) was conducted on Agela Technologies silica gel glass plates coupled with detection using ceric ammonium molybdate (CAM) and/or exposure to iodine vapor. For each derivatization the samples were placed in autosampler vials and shaken at room temperature using a Glas-Col shaker (Terre Haute, IN.). ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz) and ^{13}C-DEPT NMR (150 MHz) spectra were recorded in $CDCl_3$ unless otherwise specified. Spectra were obtained using a Bruker Avance III 600 MHz instrument equipped with a Bruker TCI 5 mm cryoprobe (Bruker Biospin, Billerica, MA) at 30.0 ± 0.1 ºC. NMR data is reported as follows: chemical shift (δ) (parts per million, ppm); multiplicity: d (doublet), t (triplet), q (quartet), quin (quintet), sex

(sextet), sep (septet), non (nonet) and br (broad); coupling constants (*J*) are given in Hertz (Hz). ^{1}H NMR chemical shifts are calibrated with respect to residual chloroform in $CDCl_3$ centered at 7.26 ppm, whereas for ^{13}C NMR, the center peak for $CDCl_3$, centered at 77.0 ppm, was used for the calibration. For the reductive aminations, refluxing was accomplished by circulating a 1:1 H_2O:ethylene glycol (maintained at 8 °C) through a 12-inch condenser using a DC30 Thermo-Haake circulating bath.

Synthesis of *β*-amino alcohols

Amino alcohols **14-16** were synthesized via the reductive amination of an aldehyde in the presence of a *N*-monosubstituted 2-aminoethanol (Scheme 2). The reaction provided high yields (85-94%) of the target *N,N*-substituted *β*-amino alcohols as light amber/brown liquids after purification by column chromatography. Their individual syntheses and structural data are given below.

<Scheme 2>

***N,N*-dipropyl-2-aminoethanol (14).** *N*-propyl-2-aminoethanol (5.12 mL, 4.6 g, 44.4 mmol) was taken up in MeOH (30 mL) in a 100 mL RB flask equipped with a stir bar. Propionaldehyde (5.92 mL, 4.8 g, 66.6 mmol, 1.5 equiv. to amine) was added via syringe and the resulting colorless solution was stirred at ambient temperature for 3 h. After this time, the solution was cooled to 0 °C and treated with $NaCNBH_3$ (3.9 g, 62.2 mmol, 1.4 equiv. to aldehyde) in small portions. The resulting solution was refluxed at 72 °C overnight. The following day, the dark

brown mixture was cooled to ambient temperature, transferred to a separatory funnel and partitioned (CH_2Cl_2//H_2O). The organic phase was copiously washed with brine (NaCl/H_2O, 3 x 100 mL), dried over Na_2SO_4 and evaporated *in vacuo* at 65 ^oC to give a light brown residue that was purified by flash column chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2:NH_3/MeOH) to furnish **14** as a light amber liquid (6.05 g, 94%). R_f = 0.40 (1:9 MeOH/CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 3.59 (t, *J* = 5.4, 2H); 3.21 (br, 1H, *OH*); 2.68 (t, *J* = 5.4, 2H); 2.52 (app t, *J* = 7.8, 4H); 1.52 (sex, *J* = 5.4, 4H); 0.90 (t, *J* = 7.2, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 57.99 (Et<u>*C*</u>H_2N x 2), 55.75 (N<u>*C*</u>H_2CH_2OH), 55.57 (NCH_2<u>*C*</u>H_2OH), 19.78 (CH_3<u>*C*</u>H_2CH_2N x 2), 11.64 (<u>*C*</u>$H_3CH_2CH_2N$ x 2); GC-HRMS (EI^+) calcd for $C_8H_{19}NO$ $[M]^{+\bullet}$ 145.1467, found 145.1469.

***N*-propyl-*N*-isopropyl-2-aminoethanol (15).** *N*-propyl-2-aminoethanol (3.0 mL, 2.7 g, 26.4 mmol) was taken up in MeOH (30 mL) in a 100 mL RB flask equipped with a stir bar. Acetone (2.9 mL, 2.3 g, 39.6 mmol, 1.5 equiv. to amine) was added via syringe and the resulting colorless solution was stirred at ambient temperature for 3 h. After this time, the solution was cooled to 0 ^oC and treated with $NaCNBH_3$ (2.32 g, 37 mmol, 1.4 equiv. to aldehyde) in small portions. The resulting dark brown solution was refluxed at 72 ^oC overnight. The following day, the mixture was cooled to ambient temperature, transferred to a separatory funnel and partitioned (CH_2Cl_2//H_2O). The organic phase was copiously washed with brine (NaCl/H_2O, 3 x 100 mL), dried over Na_2SO_4 and evaporated *in vacuo* at 55 ^oC to give a dark brown residue that was purified by flash chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2:NH_3/MeOH) to furnish **15** as a light amber liquid (3.3 g, 86%). R_f = 0.39 (1:9 MeOH/CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 3.51 (t, *J* = 5.4, 2H); 3.17 (br, 1H, *OH*); 2.99 (sep, *J* = 6.6, 1H); 2.57 (t, *J* = 5.4, 2H); 2.39 (t, *J* = 7.2, 4H); 1.45 (sex, *J* = 7.8, 2H); 1.07 (d, *J* = 7.2, 6H); 0.88 (t, *J* = 7.2, 3H); ^{13}C NMR (151 MHz,

$CDCl_3$) δ 58.18 (Et<u>*C*</u>H_2N), 51.73 (N<u>*C*</u>H_2CH_2OH), 50.69 (NCH_2<u>*C*</u>H_2OH), 50.16 (Me_2<u>*C*</u>HN), 22.00 (CH_3<u>*C*</u>H_2CH_2N), 18.03 (<u>*Me*</u>$_2$CHN), 11.68 (<u>*C*</u>$H_3CH_2CH_2N$); GC-HRMS (EI^+) calcd for $C_8H_{19}NO$ $[M]^{+\bullet}$ 145.1467, found 145.1468.

_N_-ethyl-_N_-isobutyl-2-aminoethanol (16). *N*-ethyl-2-aminoethanol (5.1 mL, 4.65 g, 52.2 mmol) was taken up in MeOH (30 mL) in a 100 mL RB flask equipped with a stir bar. Isobutyraldehyde (7.14 mL, 5.64 g, 78.3 mmol, 1.5 equiv. to amine) was added via syringe and the resulting colorless solution was stirred at ambient temperature for 3 h. After this time, the solution was cooled to 0 ^oC and treated with $NaCNBH_3$ (6.87 g, 109.6 mmol, 1.4 equiv. to aldehyde) in small portions. The resulting light brown solution was refluxed at 72 ^oC overnight. The following day, the mixture was cooled to ambient temperature, transferred to a separatory funnel and partitioned (CH_2Cl_2//H_2O). The organic phase was copiously washed with brine (NaCl/H_2O, 4 x 100 mL), dried over Na_2SO_4 and evaporated *in vacuo* at 55 ^oC to give a dark brown residue that was purified by flash chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2:NH_3/MeOH) to furnish **16** as a light brown liquid (6.43 g, 85%). R_f = 0.33 (1:9 MeOH/CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 3.50 (t, *J* = 5.4, 2H); 3.00 (br, 1H, *OH*); 2.54 (t, *J* = 5.4, 2H); 2.51 (q, *J* = 6.6, 2H); 2.17 (d, *J* = 7.2, 2H); 1.72 (non, *J* = 7.2, 1H); 1.00 (t, *J* = 6.6, 3H); 0.87 (d, *J* = 7.2, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 62.02 (Me_2CH<u>*C*</u>H_2N), 58.28 (N<u>*C*</u>H_2CH_2OH), 55.48 (NCH_2<u>*C*</u>H_2OH), 47.55 (N<u>*C*</u>H_2CH_3), 26.42 (Me_2<u>*C*</u>HCH_2N), 20.80 (*Me*$_2$CH), 11.59 (<u>*C*</u>H_3CH_2N); GC-HRMS (EI^+) calcd for $C_8H_{19}NO$ $[M]^{+\bullet}$ 145.1467, found 145.1469.

Derivatization of the β-amino alcohols

Alcohol stock solutions were prepared by dissolving the *β*-amino alcohol (100 μL) in 1 mL anhydrous methylene chloride. Additionally, a stock solution of DMAP was prepared by dissolving 14 mg of the base in 10 mL of anhydrous methylene chloride, yielding a 11.5 mM DMAP solution. For the derivatization, 100 μL of each *β*-amino alcohol stock solution was placed in a 2 mL glass autosampler vial and treated sequentially with the nitrogenous base (in the case of pyridine and NMI, 50 μL of the neat base was used, while in the case of DMAP, 50 μL of the stock solution was added), followed by phenyldimethylsilyl chloride (50 μL). The resulting mixture was shaken for 30 minutes at room temperature (24 ^{o}C), followed by the addition of anhydrous methylene chloride to bring the total volume to 1 mL and analyzed by electron impact gas chromatography-mass spectrometry (EI GC-MS). A 1 μL aliquot of the final, diluted sample was injected in the GC-MS for analysis.

Mass Spectrometry Analysis

An Agilent 7890 GC with a 5975C MS detector equipped with a split/splitless injector was used for the analysis. The GC column used for the analysis was an Agilent HP-5MS uI (5% diphenyl, 95% dimethyl polysiloxane) capillary column (30 m x 0.25 mm i.d. x 0.25 μm film) was used for the analysis. Ultra high purity helium was used as the carrier gas at 0.8 mL/min. The injector temperature was 250 °C, and the injection volume was 1 μL. The oven temperature program was as follows: the initial oven temperature was 40 °C, held for 1 min, followed by an 10 °C/min to 150 °C, then ramped at 25 °C/min to a final oven temperature of 300 °C. The MS detector ion source and quadrupole temperatures were 230 °C and 150 °C, respectively. Energy of 70 eV was used to carry out the electron impact ionization.

RESULTS AND DISCUSSIONS

Three nitrogenous bases (pyridine, NMI, and DMAP) were evaluated for their ability to promote silylation of *β*-amino alcohols in the presence of phenyldimethylsilyl chloride (PDMSCl). The efficiency of the silylation depended on the base used and the nature of the alcohol subjected to the derivatization. It was found that not all three bases performed equally in the derivatization reaction while some *β*-amino alcohols remained virtually unreactive towards these silylation conditions (*vide infra*). Table 1 provides a list of the ten *β*-amino alcohols and their PDMS derivatives along with their GC-MS information. Structurally, the *β*-amino alcohols analyzed in this work can be grouped into three categories based on their association to a chemical agent. Thus, *β*-amino alcohols **12** and **13** are products that directly arise from the oxidative degradation of the organophosphorus-based nerve agents VX and VR respectively. Alcohols **11**, and **14-16** are isomerically and chromatographically similar species to **12** and **13**. Alcohols **17-19** are the end products from the hydrolysis of the three most common nitrogen-based mustards HN2, HN1 and HN3 respectively. Lastly, *β*-amino alcohol **20** is a particularly interesting species in that it exhibits a bicyclic framework and is the major product arising from the degradation of the incapacitating agent 3-quinuclidinyl benzilate (**10**) [27-29].

<Table 1>

Analysis of the GC-MS chromatographs leads to the general consensus that pyridine and DMAP are more effective than NMI in promoting the derivatization of *β*-amino alcohols as highlighted in Figure 3. Furthermore, qualitative comparison between pyridine and DMAP indicates that

pyridine outperforms DMAP in most derivatizations that were carried out as shown in Figures 4-6. The methodology presented herein has proven effective at derivatizing the majority of the alcohols studied with the exception of triethanolamine (**19**) and 3-quinuclidinol (**20**). Therefore, amongst the bases studied it appears that pyridine and its more nucleophilic analog, DMAP, perform better than NMI, with pyridine being the best overall performer. Besides its superior performance, additional qualities that make pyridine a convenient choice for the silylation is its liquid state at room temperature, thus obviating the need for stock solution preparation as in the case of DMAP [30].

<Figure 3>

<Figure 4>

<Figure 5>

<Figure 6>

Our approach was successful in producing PDMS derivatives of certain β-amino alcohols that exhibit unique retention times within similarly structured analogs and very distinct from the parent, underivatized alcohol (Table 1). Although these alcohols display a diverse array of structural complexity, two main fragmentation patterns were observed for the derivatives that consistently yielded predominant signals by GC-MS (Scheme 3). A consistently observed fragmentation is indicated by the formation of a *N*,*N*-substituted methyleneiminium species that originates from the heterolytic cleavage of the α–β bond of the β-amino alcohol (Pathway A). It was found that in all the GC-MS-observable analytes, this species was the predominant and as such constituted the base peak of all spectra with the exception of amino alcohol **16**. The second

pathway involves the heterolysis cleavage of the O-Si bond to furnish a phenyldimethylsilyl cationic species that is readily visible in the spectrum (*m/z* = 135) (Pathway B). In most cases, this second species was the second most intense peak in the mass spectra of the analyzed derivatives (Table 1). Additional fragments that are common among the derivatized *β*-amino alcohols arise from the loss of a methyl group ($[M-15]^+$) from the silyl group, and loss of an alkyl group from the methyleneiminium ion initially formed via Pathway A.

<Scheme 3>

A more detailed discussion of each analyte studied using this derivatization technique is granted as the fragmentation patterns observed from the derivatives can be rationalized based on their structural features. Starting with the simplest, derivatized analyte, *N,N*-dimethyl-*β*-amino alcohol-PDMS **21**, one can observe the presence of the molecular ion peak (*m/z* = 223) in addition to peaks arising from the loss of a methyl group (*m/z* = 208) as well as fragments resulting from bond cleavage governed by pathways A (*m/z* = 58) and B (*m/z* = 135) (Figure 3). For its homologous counterparts **22**-**26**, additional ions can be observed, depending on the level of isomerism in the alkyl chains associated with the amino group. Thus, for *N,N*-diethyl-*β*-amino alcohol-PDMS **22**, in addition to the molecular ion peak (*m/z* = 251) and fragments arising from the loss of a methyl (*m/z* = 236), methyleneiminium ion (*m/z* = 86) and the phenyldimethylsilyl cation (*m/z* = 135), one can also identify a peak arising from the loss of an ethyl group from the methyleneiminium ion (*m/z* = 58) (Figure 7, SI). Compounds **23** through **26** offer an interesting additional level of complexity as these are now higher in molecular weight than **21** or **22** and are interrelated via structural isomerism. The chromatograph of *N,N*-

diisopropylaminoethanol-PDMS (**23**) exhibits the molecular ion peak (*m/z* = 279) and fragments arising from the loss of a methyl group (*m/z* = 264), *N*,*N*-diisopropylmethyleneiminium ion (*m/z* = 114) and the phenyldimethylsilyl cation (*m/z* = 135). In addition, the fragment arising from an isopropyl group loss from the *N*,*N*-diisopropylmethyleneiminium ion is also observed (*m/z* = 72) for alcohol **23** (Figure 4). *N*,*N*-dipropyl-*β*-amino alcohol **24** possesses a unique fragmentation pattern in addition to its molecular ion (*m/z* = 279), methyl group loss (*m/z* = 264), *N*,*N*-dipropylmethyleneiminium ion (*m/z* = 114) and the phenyldimethylsilyl cation (*m/z* = 135). For example, those arising from loss an ethyl group from the molecule (*m/z* = 250) as well as two ion fragments arising from the further fragmentation of its iminium ion via loss of an ethyl group (*m/z* = 86) and a propyl group (*m/z* = 72) (Figure 8, SI). In addition to signals common to the *β*-amino alcohols so far discussed, *N*-propyl-*N*-isopropylaminoethanol derivative **25** exhibits additional ions originating from loss of a methyl group from the molecule (*m/z* = 264) and one arising from the further fragmentation of its iminium ion via loss of an isobutyl group (*m/z* = 72) (Figure 5). *N*-ethyl-*N*-isobutylaminoethanol derivative **26** provides additional ion fragments arising from the loss of an isopropyl group (*m/z* = 236) from the molecular ion. Furthermore, ions arising from loss of a methyl group (*m/z* = 264) and loss of an isobutyl unit from the methyleneiminium ion (*m/z* = 58) are observed (Figure 6).

Turning our attention to the diethanolamine derivatives, it is important to state that none of the parent alcohols could be detected in their underivatized form by EI GC-MS. In these derivatives (**27**-**29**), we observe the same type of fragmentation patterns observed for the simple *β*-amino alcohol derivatives. Once again the main pathways for fragmentation involved the cleavage of the *α*–*β* bond of only one of the sides of the derivative, and cleavage of the O-Si bond to yield

the ubiquitous *m/z* = 135 ion observed for all PDMS derivatives. Unfortunately, these types of fragmentations were only readily observed for compounds **27** and **28**, the derivatives of the precursors of HN2 and HN1 respectively (Figures 9 and 10, SI). Triethanolamine (**19**) and its PDMS derivative (**29**), were not observed in our analyses (Table 1). Thus, from a derivatization standpoint, it appears that the approach works very well for the diethanolamine analytes, while other more established techniques (*e.g.* BSTFA derivatization) might be needed to derivatize this compound. Lastly, the 3-quinuclidinol was not observed in either its intact or derivatized form (**30**). This can be attributed to the observation that the 3-quinuclidinol was only sparingly soluble in methylene chloride, needing gentle heating and vigorous shaking. Nevertheless, the alcohol was never fully dissolved, with the suspension eventually providing a biphasic mixture in the autosampler vial.

CONCLUSION

The effect on the silylation of a panel of ten β-amino alcohols using phenyldimethylsilyl chloride (PDMSCl) by the addition of a nitrogenous base such as pyridine, *N*-methylimidazole (NMI) and 4-dimethylaminopyridine (DMAP) was evaluated. The use of the base as an additive in the reaction allows for the silylation to be conveniently carried out at ambient temperature and in less than 30 minutes. All the β-amino alcohols examined were smoothly silylated with the exceptions of triethanolamine and 3-quinuclidinol, likely due to their poor solubility in the reaction medium. In addition to providing strong, common fragment ions such as the methyleneiminium ion arising from lysis of the α–β bond and the phenyldimethylsilyl cation (m/z = 135), the silylated β-amino alcohols also yielded signature fragmentation patterns directly

arising from their different *N*-alkyl groups. Furthermore, the silylated alcohols exhibited significantly higher retention times relative to their parent alcohols, with typical differences between these values lying in the range of 6.7-9.1 minutes. With regards to the bases analyzed, pyridine was found to be superior in all successful derivatizations over NMI and DMAP, making it the reagent of choice for carrying out the protocol. Thus, the methodology presented herein describes a derivatization technique for β-amino alcohols that can be performed quickly under mild conditions (room temperature). The method should find widespread use as an alternative approach to other commonly used techniques for the analysis of compounds by EI-GC-MS.

DISCLAIMER

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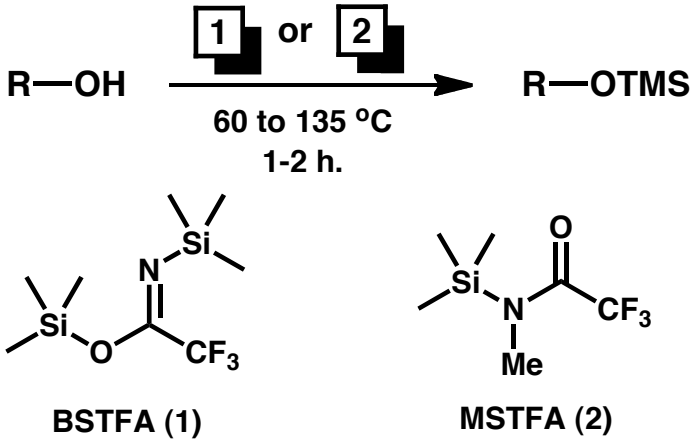
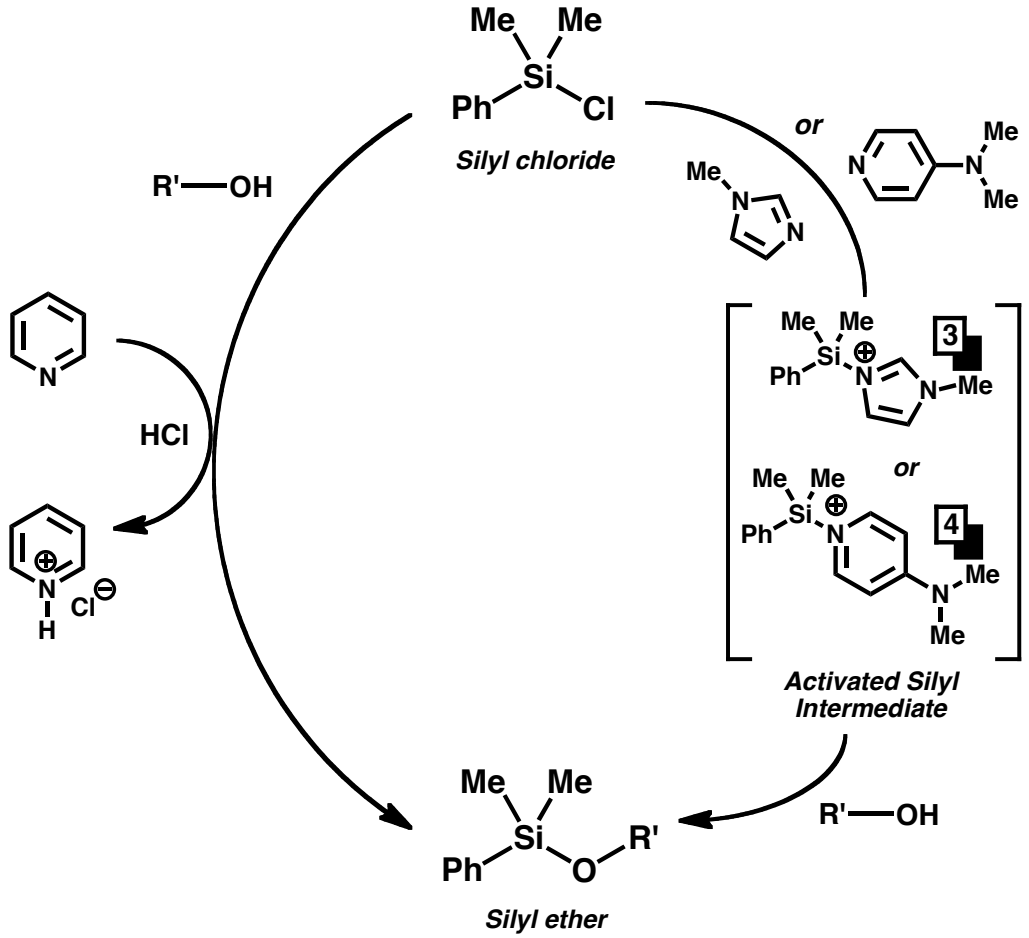
493 **Figures and Schemes**

494



495

496 **Figure 1.**



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498 **Scheme 1.**

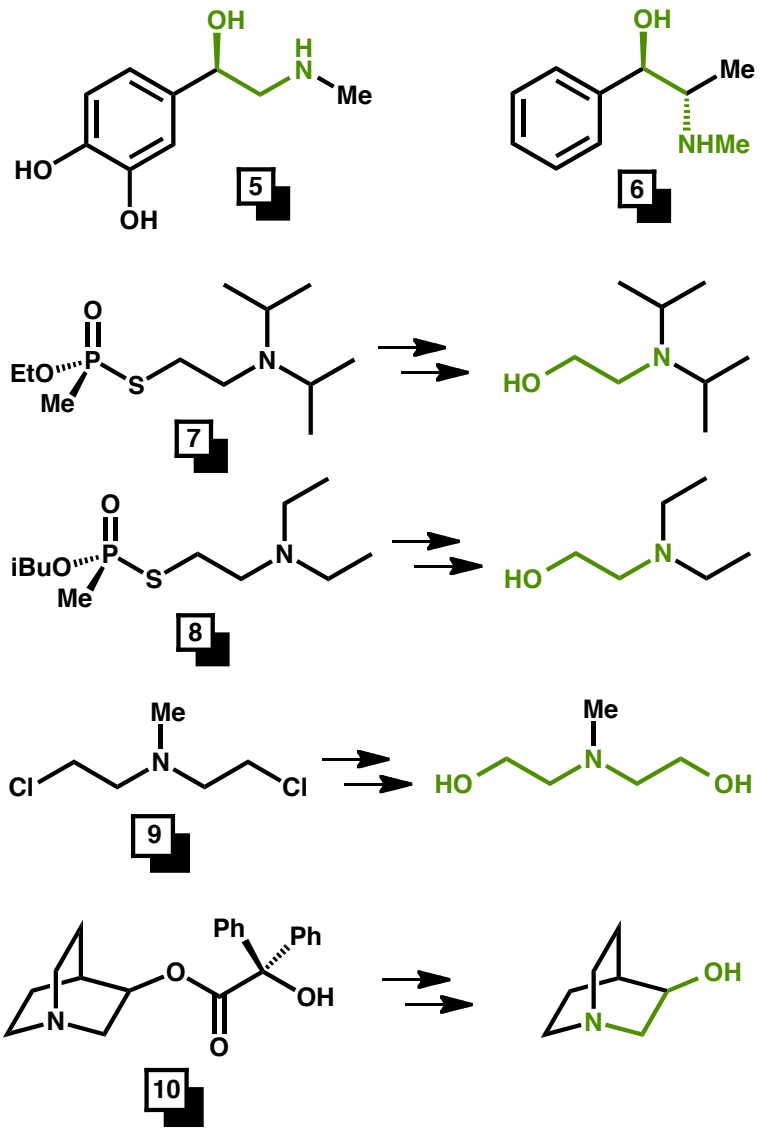
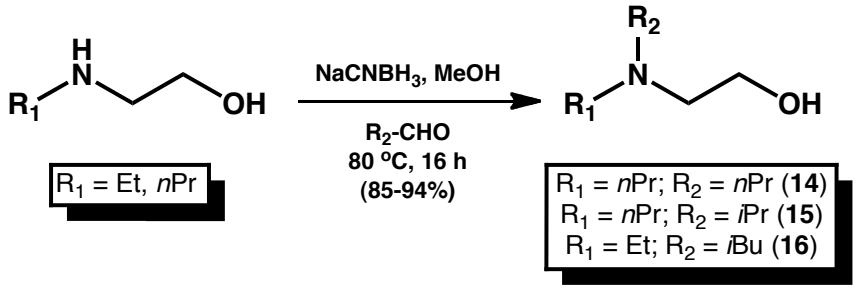


Figure 2.



Scheme 2.

β-Amino Alcohol/PDMS derivative	Ret. Time (min)	MW (g mol^{-1})	M^+ (Rel. Intensity)	$[R_1R_2NH{=}CH_2]^+$ (Rel. Intensity)[a]	$[PhMe_2Si]^+$ (Rel. Intensity)	Other Fragments (Rel. Intensity)
N,*N*-dimethylaminoethanol (**11**)	3.35[b]	89	89 (6.7)	58 (100)	--	42 (19)
N,*N*-diethylaminoethanol (**12**)	5.42[b]	117	117 (4.5)	86 (100)	--	58 (34); 102 (6.5)
N,*N*-diisopropylaminoethanol (**13**)	8.21[b]	145	145 (5.9)	114 (100)	--	72 (60.5); 102 (11.1)
N,*N*-dipropylaminoethanol (**14**)	8.59[b]	145	145 (4.4)	114 (100)	--	72 (25.3); 86 (18.0)
N-propyl-*N*-isopropylaminoethanol (**15**)	8.18[b]	145	145 (4.6)	114 (100)	--	72 (56.2); 102 (8.7)
N-ethyl-*N*-isobutylaminoethanol (**16**)	7.72[b]	145	145 (3.6)	114 (36.4)[c]	--	58 (39.7); 102 (100)
N-methyldiethanolamine (**17**)	--[d]	119	--	--	--	--
N-ethyldiethanolamine (**18**)	--[d]	133	--	--	--	--
Triethanolamine (**19**)	--[d]	149	--	--	--	--
3-Quinuclidinol (**20**)	--[d]	127	--	--	--	--
N,*N*-dimethylaminoethanol-PDMS (**21**)	12.43	223	223 (4.1)	58 (100)	135 (8.7)	105 (6.7); 208 (2.9)
N,*N*-diethylaminoethanol-PDMS (**22**)	13.70	251	251 (2.0)	86 (100)	135 (8.2)	58 (5.3)
N,*N*-diisopropylaminoethanol-PDMS (**23**)	14.51	279	279 (1.5)	114 (100)	135 (8.5)	72 (15.7); 264 (3.4)
N,*N*-dipropylaminoethanol-PDMS (**24**)	14.63	279	279 (2.6)	114 (100)	135 (12.0)	72 (3.4); 250 (7.5)
N-propyl-*N*-isopropylaminoethanol-PDMS (**25**)	14.57	279	279 (1.5)	114 (100)	135 (10.1)	72 (15.7); 264 (3.8)
N-ethyl-*N*-isobutylaminoethanol-PDMS (**26**)	14.41	279	279 (0.6)	114 (100)	135 (20.4)	58 (17.0); 236 (26.0)
N-methyldiethanolamine-PDMS (**27**)	17.38	387	387 (0.5)	222 (100)	135 (63.1)	130 (27.4)
N-ethyldiethanolamine-PDMS (**28**)	17.51	401	401 (0.6)	236 (100)	135 (64.8)	120 (6.5); 144 (20.0)
Triethanolamine-PDMS (**29**)	--[e]	551	--	--	--	--
3-Quinuclidinol-PDMS (**30**)[c]	--[e]	261	--	--	--	--

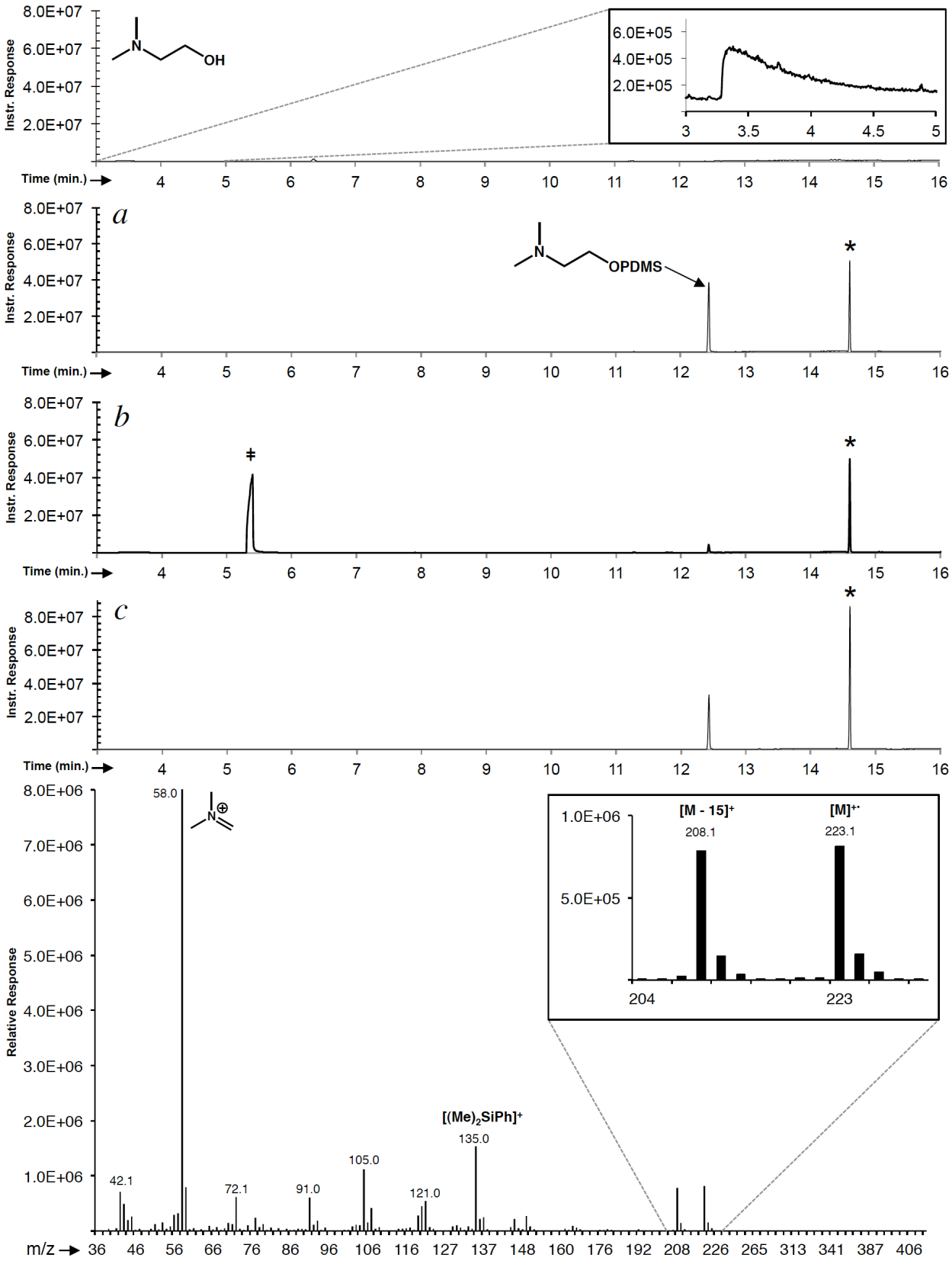

Instr. Response
Time (min.)
OH
OPDMS
a
b
c
‡
*
Relative Response
m/z
58.0
42.1
72.1
91.0
105.0
121.0
135.0
[(Me)2SiPh]+
[M - 15]+
208.1
[M]+·
223.1
204
223

Figure 3.

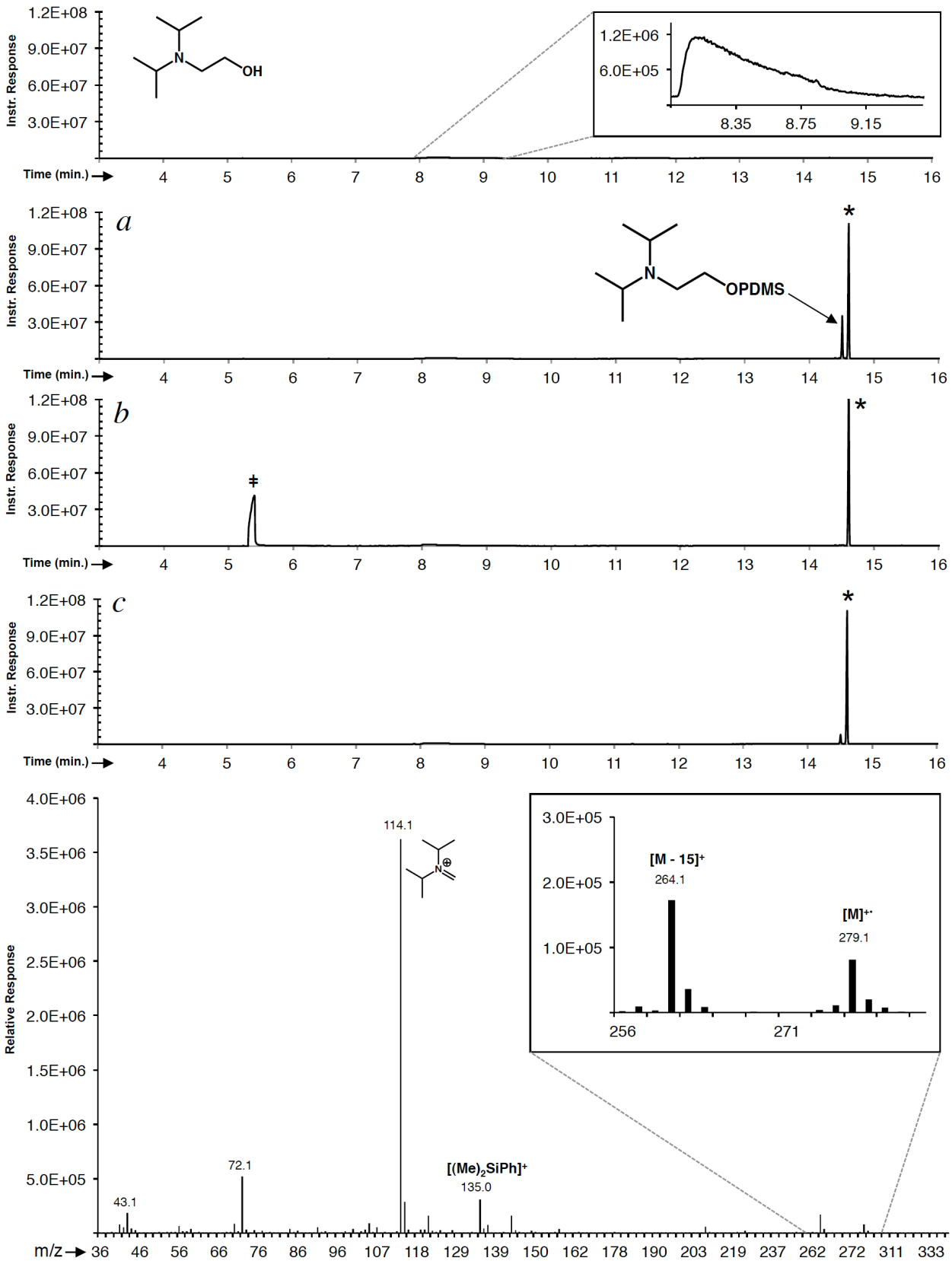

1.2E+08
9.0E+07
6.0E+07
3.0E+07
Instr. Response
Time (min.)
4 5 6 7 8 9 10 11 12 13 14 15 16
OH
1.2E+06
6.0E+05
8.35 8.75 9.15
a
OPDMS
*
b
‡
*
c
*
4.0E+06
3.5E+06
3.0E+06
2.5E+06
2.0E+06
1.5E+06
1.0E+06
5.0E+05
Relative Response
114.1
72.1
43.1
[(Me)2SiPh]+
135.0
3.0E+05
2.0E+05
1.0E+05
[M - 15]+
264.1
[M]+·
279.1
256
271
m/z
36 46 56 66 76 86 96 107 118 129 139 150 162 178 190 203 219 237 262 272 311 333

Figure 4.

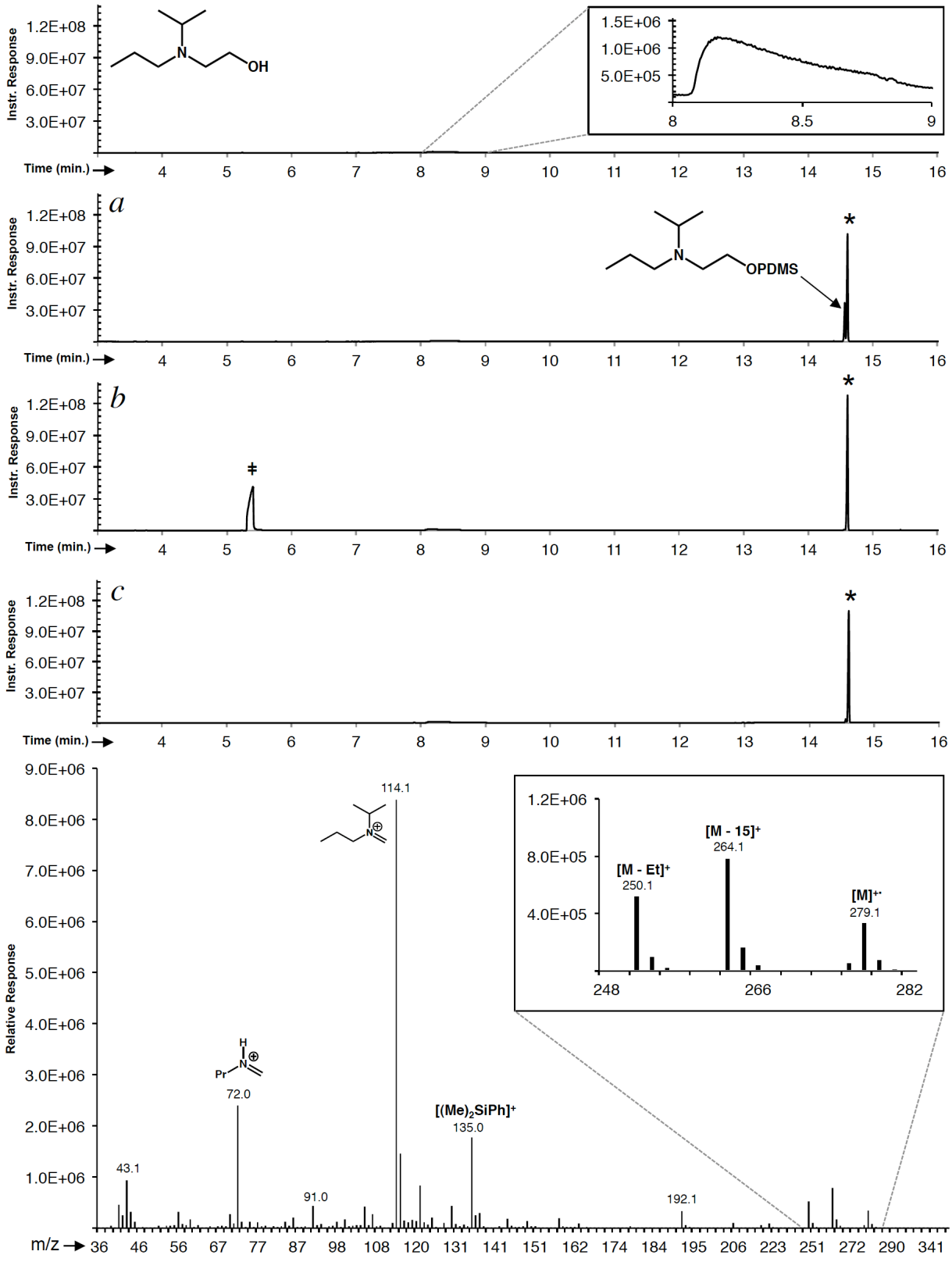

Instr. Response
Time (min.)
OH
OPDMS
a
b
c
*
‡
Relative Response
m/z
114.1
72.0
[(Me)2SiPh]+
135.0
43.1
91.0
192.1
[M - Et]+
250.1
[M - 15]+
264.1
[M]+·
279.1

Figure 5.

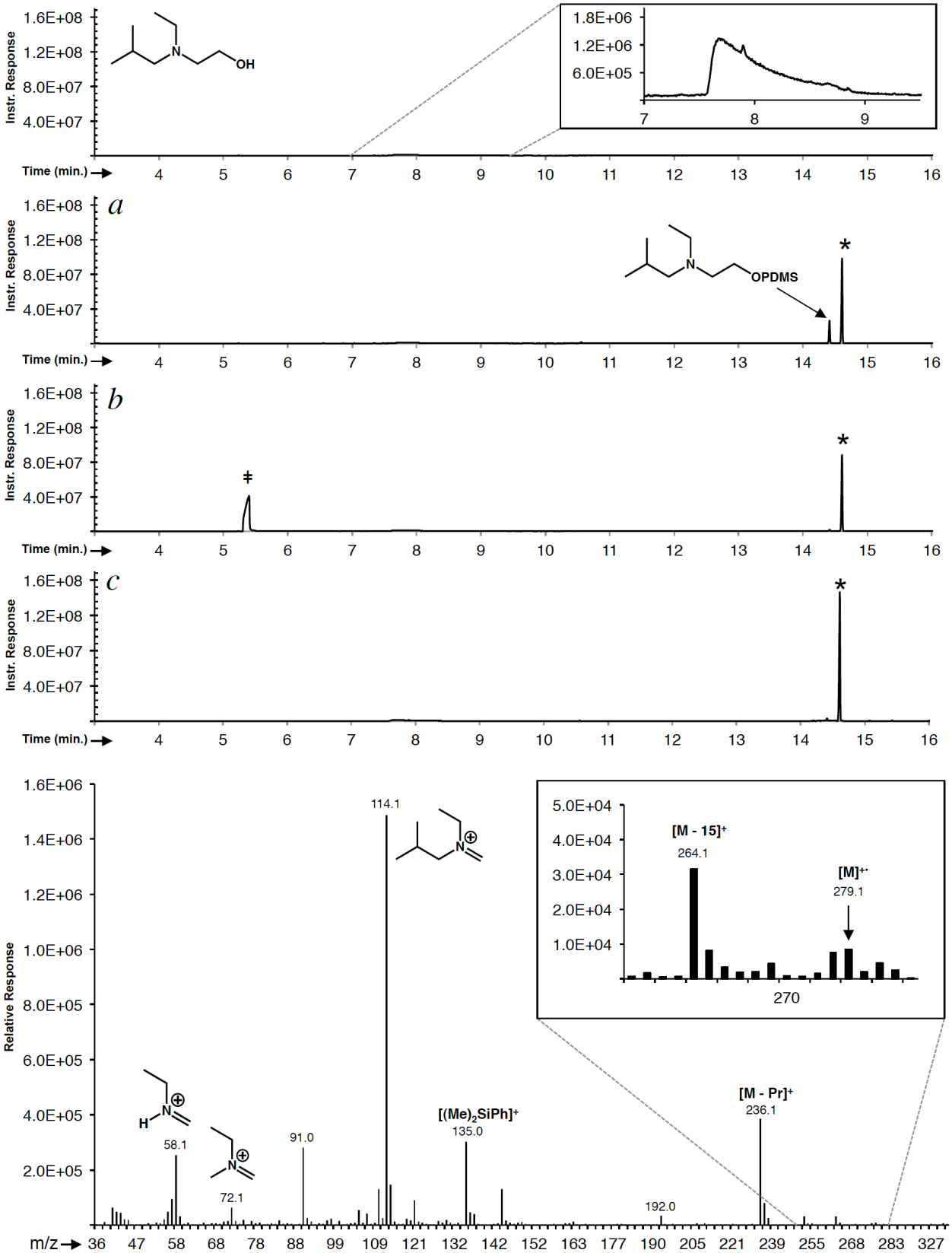
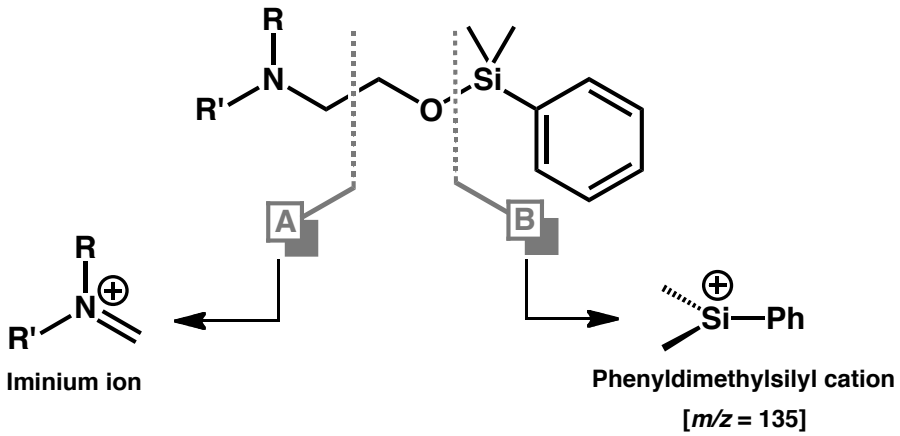

Instr. Response
Time (min.)
OH
OPDMS
a
b
c
‡
*
Relative Response
m/z
114.1
58.1
72.1
91.0
[(Me)2SiPh]+
135.0
192.0
[M - Pr]+
236.1
[M - 15]+
264.1
[M]+·
279.1
270

Figure 6


R
N
R'
O
Si
A
B
R
N
R'
Iminium ion
Si—Ph
Phenyldimethylsilyl cation
[m/z = 135]

Scheme 3.

Figures/Schemes Captions

Figure 1. Conditions for the derivatization of an alcohol with BSTFA and MSTFA.

Scheme 1. Proposed routes for the silylation reaction in the presence of pyridine, NMI and DMAP.

Table 1. *a*. Fragment arises from the heterolysis of the α–β bond in the β-aminoalcohol and its PDMS derivative; *b*. Broad signal; *c*. Base peak was *m/z* = 102; *d.* not detected; *e.* no detection of the PDMS derivative possibly due to the poor solubility of the aminoalcohol.

Scheme 2. Synthesis of β-amino alcohols **14-16**.

Scheme 3. Dominant fragmentation pathways for the β-amino alcohols and their PDMS derivatives studied.

Figure 2. Presence of the β-aminoethanol motif in several compounds, and their presences as indicating species for the presence of CWAs. The motif is highlighted in light green in the structures above.

Figure 3. Chromatograph showing the derivatization of *N*,*N*-dimethylaminoethanol **11** in the presence of *a*) pyridine, *b*) NMI and *c*) DMAP. The last section shows the mass spectrum for PDMS-derivative **21**. (*****= 1,3-dichloro-1,3-diphenyl-1,1,3,3-tetramethyldisiloxane; ≠ = NMI).

Figure 4. Chromatograph showing the derivatization of *N,N*-diisopropylaminoethanol (**13**) in the presence of *a*) pyridine, *b*) NMI and *c*) DMAP. The last section shows the mass spectrum for PDMS-derivative **23**. (*****= 1,3-dichloro-1,3-diphenyl-1,1,3,3-tetramethyldisiloxane; ≠ = NMI).

Figure 5. Chromatograph showing the derivatization of *N*-propyl-*N*-isopropylaminoethanol (**15**) in the presence of *a*) pyridine, *b*) NMI and *c*) DMAP. The last section shows the mass spectrum for PDMS-derivative **25**. (*****= 1,3-dichloro-1,3-diphenyl-1,1,3,3-tetramethyldisiloxane; ≠ = NMI).

Figure 6. Chromatograph showing the derivatization of *N*-ethyl-*N*-isobutylaminoethanol (**16**) in the presence of *a*) pyridine, *b*) NMI and *c*) DMAP. The last section shows the mass spectrum for PDMS-derivative **26**. (*****= 1,3-dichloro-1,3-diphenyl-1,1,3,3-tetramethyldisiloxane; ≠ = NMI).