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The Henry Reaction: Spectroscopic Studies of Nitrile and Hydroxylamine By-products Formed During Synthesis of Psychoactive Phenylalkylamines

Research Article

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Abstract: A clandestine two-step route to psychoactive racemic phenylalkylamines utilises the Henry reaction. In the first step an aromatic aldehyde reacts with a nitroalkane to give the nitrostyrene intermediate. In the second step the nitrostyrene is reduced to the phenylalkylamine. An impurity profile of both steps was evaluated through the synthesis and analysis of common street derivatives. The formation of nitrile impurities in the nitroaldol reaction and hydroxylamine impurities in the reduction step were shown by NMR spectroscopy and GC-MS. A selection of reducing agents has been used to give the phenylalkylamines, together with variable quantities of the partially reduced hydroxylamine product. GC-MS analysis of the hydroxylamines showed heat-induced disproportionation which led to the detection of the corresponding oximes.

Keywords: *Drugs of abuse • Impurities • Amphetamines • NMR • GC-MS*

1. Introduction

The Henry reaction is exemplified by the preparation of (*E*)-nitrostyrene derivatives in which a C-C bond is formed by a nitroaldol reaction to give a nitroalcohol intermediate. The presence of acid facilitates subsequent antiperiplanar elimination of water which provides the nitroalkene product [1]. Nitrostyrene derivatives are useful synthetic intermediates and are increasingly evaluated for their medicinal potential properties, for example, antibacterial [2] or antiplatelet activities [3].

The reduction of the nitrostyrenes gives access to a large number of phenylalkylamines with psychoactive properties in humans [4]. Representative examples include amphetamine stimulants unsubstituted on the benzene ring, 3,4-methylenedioxy-containing entactogens such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) [5] and methoxylated hallucinogens such as 2,5-dimethoxy-4-iodoamphetamine (DOI) [6]. Approximately 200 phenylalkylamines have been synthesised and their effects described by Shulgin and Shulgin [7]. Freeman and Alder have published an overview detailing common synthetic routes to the phenylalkylamine [8].

A great number of phenylalkylamines are consumed within a recreational context where the lack of quality control often results in poorly characterised products with

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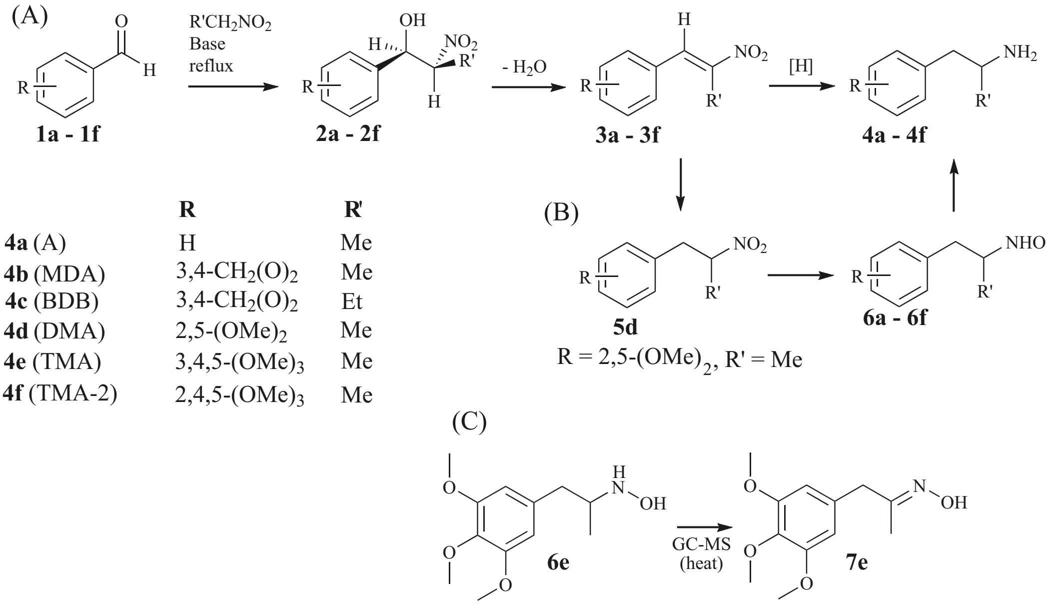

	R	R'
4a (A)	H	Me
4b (MDA)	$3,4\text{-}CH_2(O)_2$	Me
4c (BDB)	$3,4\text{-}CH_2(O)_2$	Et
4d (DMA)	$2,5\text{-}(OMe)_2$	Me
4e (TMA)	$3,4,5\text{-}(OMe)_3$	Me
4f (TMA-2)	$2,4,5\text{-}(OMe)_3$	Me

Figure 1. **(A)** Henry reaction: the synthesis of (*E*)-nitrostyrene derivatives **3a-3f** was based on the use of appropriately substituted benzaldehyde starting materials **1a-1f**. C-C bond formation was base catalysed in order to facilitate conversion to nitroalcohol intermediates **2a-2f** (not isolated), followed by proton abstraction and elimination of water. The desired phenylalkylamines **4a-4f** were prepared by reduction of their nitroalkene precursors using several different reducing agents. Compound abbreviations: A: amphetamine; MDA: 3,4-methylenedioxyamphetamine; BDB: 1-(3',4'-methylenedioxyphenyl)butan-2-amine; DMA: 2,5-dimethoxyamphetamine; TMA: 3,4,5-trimethoxyamphetamine; TMA-2: 2,4,5-trimethoxyamphetamine. (**B**) Incomplete reduction to the nitroalkane (**5d**) was observed after the reduction of (**3d**) with $NaBH_3CN$. (**C**) Representative example of a heat-induced disproportionation of hydroxylamine side products during GC-MS analysis.

unknown toxicology. The profiling and fingerprinting of illegal amphetamine and MDMA preparations is routinely carried out by gas chromatography-mass spectrometry (GC-MS) [9-11]. One important application is found within a forensic and clinical context where the presence or absence of specific impurities (markers) can help to determine the route of synthesis and precursor(s) used [8]. Unambiguous identification of by-products can be a challenge if MS detection is solely involved, particularly if structural isomers are present, since they often give rise to identical fragmentation patterns. Under these conditions, the combined use of NMR spectroscopy can facilitate impurity identification.

In this study, emphasis was placed on the application of $^1H/^{13}C$ NMR spectroscopy and GC-MS analysis to the preparation of phenylalkylamines **4a-4f** (Fig. 1 (A)), selected due to their potential recreational use [7]. In addition several reducing agents were used for the conversion of the nitrostyrenes into the desired amine products in order to evaluate product purity.

2. Experimental Procedures

All chemicals and reagents were obtained from the Aldrich Chemical Company or Lancaster Chemical Company with the exception of nitromethane and formamide from BDH, d_6-DMSO from Cambridge Isotope Laboratories Inc., ammonium acetate and ninhydrin from Fluka and D_2O from Goss Scientific Instruments Ltd. All experiments were performed in clean, oven-dried glassware under nitrogen. Solvents used were anhydrous or dried as appropriate.

TLC was performed using VWR plates coated with silica gel 60, containing F_{254} and visualised by using a UV light source at 254 nm or dipping with $KMnO_4$. Amines were visualised using a ninhydrin dip (10% solution in ethanol). Flash column chromatography was performed under pressure using VWR silica gel, particle size 33-70 μm [12].

NMR spectra were obtained using a Bruker Advance 300 MHz spectrometer and data was manipulated using X-Win software. ^1H, ^{13}C and ^{31}P NMR spectra were recorded at 300, 75 and 121.5 MHz, respectively. The NMR solvent $CDCl_3$ was used with TMS as a reference at 0 ppm. Spectra obtained in D_2O used sodium 3-(trimethylsilyl)-propionic acid-d_4 (TSP) as reference at 0 ppm or benzene referenced to 7.27 ppm for ^1H NMR and 128.5 ppm for ^{13}C NMR spectra. Coupling constants (J) are expressed in Hz. ^{13}C NMR spectra were assigned with the aid of DEPT-135 spectra.

IR spectra were recorded using a Bruker Tensor 27 (resolution 4 cm^{-1}, 32 scans per sample) and Opus software. Absorbance peaks were recorded at the relevant wavenumber (cm^{-1}). Mass analyses were performed in the School of Chemistry, University of Manchester, using electron ionisation (EI), positive chemical ionisation (CI, using NH_3). An automated Fisons TR10 2000 quadrupole spectrometer was used for direct infusion analysis.

GC-MS conditions (A): Electron- and chemical ionisation mass spectra were obtained on a Varian Saturn 2200 ion trap MS equipped with a Varian CP-3800 gas chromatograph (Varian, USA) and a Combi Pal autosampler (CTC Analytics, Switzerland). Data handling was completed with Saturn GC/MS Workstation, Version 5.52 software. A 5% phenyl, 30 m × 0.25 mm CP-Sil 8 CB Low Bleed/MS column with a film thickness of 0.25 µm was used. The column temperature was programmed as follows: 40ºC and hold 1 min, then heat at 50ºC min^{-1} to 260ºC and held at this temperature for 14.6 min. Total run time was 20 min. A CP-1177 injector (280ºC) was used in the split mode with a 50:1 split. The carrier gas was helium at a flow rate of 1 ml min^{-1} (EFC constant flow mode). The transfer line, manifold and ion trap temperatures were set to 270, 95 and 200ºC, respectively. HPLC grade methanol was used as the liquid CI reagent. Ionisation parameters (0.5 s scan^{-1}): CI storage level: 19.0 m/z, ejection amplitude: 15.0 m/z, background mass: 55 m/z, maximum ionisation time: 2000 µs, maximum reaction time: 40 ms and target TIC: 5000 counts. CI-MS-MS spectra were obtained by collision induced dissociation (CID) of the protonated molecule $[M+H]^+$ within the ion trap, using helium, by application of a CID waveform excitation amplitude in the non-resonant mode. Excitation storage level was set to 48.0 m/z and the excitation amplitude was set to 20V. The number of ions (target TIC) in the trap was controlled by an automatic gain control function.

GC-MS conditions (B): Individual electron ionisation mass spectra were obtained using a Fisons MD800 quadrupole mass spectrometer following chromatographic separation with a Fisons 8000 series temperature programmed gas chromatographic oven. MassLab, Version 1.3, software was used for instrument control and data handling. A VF-5ms 30 m × 0.25 mm Low Bleed MS Varian column having a film thickness of 0.25 µm was used to afford separation. The column temperature was programmed from 70ºC and held for 1 min, then heated at 8ºC min^{-1} to 220ºC and held at this temperature (variable time). One µl volumes of sample were injected manually, in splitless mode, with the injector temperature held at 180ºC. The carrier gas was helium at a flow rate of 1 ml min^{-1}. The transfer line was set to 270ºC.

2.1. Synthesis of nitrostyrenes using the Henry reaction

(*E*)-2-nitro-1-phenylprop-1-ene (**3a**), (*E*)-2-nitro-1-(3',4'-methylenedioxyphenyl)prop-1-ene (**3b**), (*E*)-2-nitro-1-(2',5'-dimethoxyphenyl)prop-1-ene (**3d**), (*E*)-2-nitro-1-(3',4',5'-trimethoxyphenyl)prop-1-ene (**3e**) and (*E*)-2-nitro-1-(2',4',5'-trimethoxyphenyl)prop-1-ene (**3f**) were prepared using the method of Shulgin and Shulgin using nitroethane and the appropriate aromatic aldehyde in glacial acetic acid, followed by cyclohexylamine [7]. Analytical data obained were all in agreement with their structures and are not reproduced here.

2-Nitro-1-(3',4'-methylenedioxyphenyl)but-1-ene (**3c**) was prepared similarly. Nitropropane (8.90 g, 99.9 mmol, 2 eq) was then added to a stirred solution of piperonal (7.50 g, 50.0 mmol, 1 eq) in glacial acetic acid (40 ml). Cyclohexylamine (4.63 g, 47.1 mmol, 1 eq) was and heated at 100ºC for 4.5 h. Column chromatography (5:1; hexane-ethyl acetate) gave bright yellow crystals (2.12 g, 9.57 mmol, 19.2%); TLC (5:1; hexane-ethyl acetate) R_f = 0.71; Mp 58-60°C, Lit mp 64-65°C [7]; δ_C ($CDCl_3$) 151.7 (C-3'), 149.4 (C-4'), 148.4 (C-NO_2), 133.3(CH), 126.1 (C-1') 125.8 (C-6'), 109.1 (C-2' or C-5'), 108.9 (C-2' or C-5'), 101.8 (OCH_2O), 20.8 (CH_2), 12.4 (CH_3); Major (*E*)-isomer: δ_H ($CDCl_3$) (97%, (*E*)-isomer confirmed by NOESY) 7.96 (1H, s, CH), 6.97 (1H, dd, $^3J_{C\text{-}6'H/C\text{-}5'H}$ = 8.1 Hz, $^4J_{C\text{-}6'H/C\text{-}2'H}$ = 1.5 Hz, C-6'H), 6.27 (1H, d, $^3J_{C\text{-}2'H/C\text{-}6'H}$ = 1.5 Hz, C-2'H), 6.89 (1H, d, $^4J_{C\text{-}5'H/C6'H}$ = 8.1 Hz, C-5'H), 6.05 (2H, s, OCH_2O), 2.88 (2H, q, $^3J_{CH2/CH3}$ = 7.4 Hz, CH_2), 1.28 (3H, t, $^3J_{CH3/CH2}$ = 7.4 Hz, CH_3); GC-MS (A) 97.7%, t_R = 8.86 min, (EI) 221 (100%, $M^{\bullet+}$), 174 (53%), 115 (68%); (CI-MS-MS) 222 (70%, $[M+H]^+$), 151 (100%), 123 (26%). Minor (*Z*)-isomer: δ_H ($CDCl_3$) (3%): 7.27 (1H, s, CH), 6.8-6.7 (3H, m, C-2'H, C5'H, C6'H), 5.97 (2H, s, OCH_2O), 2.66 (2H, dq, $^4J_{CH2/CH}$ = 1.1 Hz, $^3J_{CH2/CH3}$ = 7.4 Hz, CH_2), 1.19 (3H, t, $^3J_{CH3/CH2}$ = 7.4 Hz, CH_3); GC-MS (A) 2.3%, t_R = 8.46 min, (EI) 221 (100%, $M^{\bullet+}$), 174 (75%), 115 (90%); (CI-MS-MS): 175 (13%, $[M+H]^+$), 151 (100%), 123 (31%).

3,4-Methylenedioxybenzonitrile (**8**) was prepared as a side-product when attempting to make (*E*)-2-nitro-1-(3',4'-methylenedioxyphenyl)prop-1-ene (**3b**) using the method described by Karmarkar and colleagues [13]. Nitroethane (7.49 g, 100 mmol, 2 eq) and piperonal (7.50 g, 50.0 mmol, 1 eq) were added to a stirring solution of glacial acetic acid (10 ml). Ammonium acetate (7.71 g, 100 mmol, 1 eq) was added and the mixture was heated at 160ºC for 6.5 h. Water (15 ml) was added, the precipitate collected which was dissolved in hot toluene-hexane (1:4), filtered and cooled to give yellow needles (3.69 g). Column chromatography (5:1, hexane-ethyl acetate) gave dark yellow needles (413 mg, 2.80 mmol, 5.6%). TLC (2:1; hexane-ethyl acetate) R_f = 0.67; mp 87-88°C, Lit mp 92-93°C [14]; IR 2220 cm^{-1} (m, CN); δ_H ($CDCl_3$) 7.22 (1H, dd, $^3J_{C\text{-}6'H/C\text{-}5'H}$ 8.1 Hz, $^4J_{C\text{-}6'H/C\text{-}2'H}$ 1.6 Hz, C-6'H), 7.04 (1H, d, $^4J_{C\text{-}2'H/C\text{-}6'H}$ 1.6Hz, C-2'H), 6.87 (1H, d, $^3J_{C\text{-}5'H/C\text{-}6'H}$ 8.1 Hz, C-5'H), 6.07 (2H, s, OCH_2O); δ_C ($CDCl_3$) 151.6 (C-3'), 148.1 (C-4'), 128.2 (C-6'), 118.9 (C-1'), 111.4 (C-2' or C-5'), 109.2 (C-2' or C-5'), 105.0 (CN), 102.3 (OCH_2O).

2.2. Synthesis of the 3,4-methylenedioxybenzonitrile (8) standard

3,4-Methylenedioxybenzonitrile (**8**) was prepared in 63.5% yield by an adapted method using piperonal, hydroxylamine and cyclohexylamine in glacial acetic acid [14,15]. Pale yellow crystals were obtained. TLC (5:1; hexane-ethyl acetate) R_f 0.40; NMR data as previously stated; Mp 89-91°C; Lit mp = 92-93°C [14]; IR: 2222 cm^{-1} (m, CN).

2.3. Synthesis of phenylalkylamines by reduction of nitrostyrenes

Amphetamine HCl (**4a**) and the 1-phenylpropan-2-hydroxylamine HCl (**6a**) impurity were prepared using the method of Varma and Kabalka [16]. $NaBH_4$ (1.10 g, 29.1 mmol, 4.75 eq) and $BF_3\text{-}Et_2O$ (5.22 g, 36.8 mmol, 6 eq) in THF (66 ml) were stirred at 0°C for 10 min. At room temperature 2-nitro-1-phenylprop-1-ene (**3a**) (1.0 g, 6.13 mmol, 1 eq) in THF (15 ml) was then added dropwise and the reaction mixture heated at reflux for 3 h. The reaction mixture was left to cool at room temperature then water (75 ml), and HCl 1M (75 ml) were added. The reaction mixture was then heated at 80-85°C for 3h. The aqueous layer was washed with diethyl ether; sodium hydroxide was added until the solution was basic, NaCl solution was added and the product was extracted into diethyl ether and dried ($MgSO_4$). Evaporation of the solvent gave pale yellow oil which was dissolved in propan-2-ol, acidified and diluted with diethyl ether. Evaporation gave a yellow oil (0.82 g, 4.78 mmol, 78%). ^1H NMR spectroscopy showed the presence of amphetamine (**4a**) (80%) and 1-phenylpropan-2-hydroxylamine HCl (**6a**) (20%). Flash column chromatography eluting with ethyl acetate was performed on a batch of crude material (0.3 g, 1.75 mmol). TLC (ethyl acetate) R_f = 0.88 (**6a**), 0.34 (**4a**). A mixture of (**4a**) and (**6a**) was eluted as a brown oil (190.6 mg). MS(CI): 152 (35%, $[M+H]^+$ **6a**), 136 (100%, $[M+H]^+$ **4a**)]. Pure (**6a**) was also eluted as a brown oil (89.4 mg, 0.48 mmol, 18.2%); δ_H (D_2O + benzene) 7.50-7.32 (5H, m, aromatic CH), 3.86-3.74 (1H, m, CH), 3.18 (1H, dd, $^2J_{gem}$ = 13.8 Hz, $^3J_{CHA/CH}$ = 6.0Hz, C$\underline{\text{HA}}$CHB), 2.92 (1H, dd, $^2J_{gem}$ = 13.8 Hz, $^3J_{CHB/CH}$ = 8.4 Hz, CHAC$\underline{\text{HB}}$), 1.32 (3H, d, $^3J_{CH3/CH}$ = 6.6 Hz, CH_3); δ_C (D_2O + benzene) 135.5 (C-1'), 129.5 (C-3' or C-5'), 129.0 (C-2' or C-6'), 128.5 (C-4'), 58.9 (CH), 36.1 (CH_2), 13.4 (CH_3).

3,4-Methylenedioxyamphetamine HCl (**4b**) was prepared using the method of Shulgin and Shulgin [7]. 2-Nitro-1-(3',4'-methylenedioxyphenyl)prop-1-ene (**3b**) (3.27 g, 15.8 mmol, 1 eq) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (3.63 g, 95.7 mmol, 6 eq) in THF (45 ml). The reaction mixture was heated at reflux overnight. Propan-2-ol (20 ml), NaOH (15%, 20 ml) and water (12 ml) were added and the white solid produced was removed by filtration. The filtrate was evaporated to give a brown residue. DCM (20 ml) was added and aqueous HCl (20%) was added until the solution was acidic, the aqueous layer was then washed with DCM. Addition of NaOH (20%) until basic produced a cloudy solution that was then re-extracted with DCM, dried ($MgSO_4$), filtered and evaporated to brown oil. Propan-2-ol was added to dissolve the oil and HCl (conc.) was added until the solution was acidic. The solution was then diluted with diethyl ether (20 ml) until crystals formed, which were collected by filtration and washed with diethyl ether to give crude (**4b**) as beige crystals (1.02 g, 4.73 mmol, 29.9%). Recrystallisation from propan-2-ol yielded a brown solid (276 mg, 1.28 mmol, 8.1%). Mp 172-176°C, Lit mp 187-188°C [17]; δ_H (D_2O + TSP) 6.91 (1H, br d, $^3J_{C\text{-}5'H/C\text{-}6'H}$ = 7.9 Hz, C-5'H), 6.86 (1H, d, $^4J_{C\text{-}2'H/C\text{-}6'H}$ = 1.6Hz, C-2'H), 6.80 (1H, dd, $^3J_{C\text{-}6'H/C\text{-}5'H}$ = 7.9 Hz, $^4J_{C\text{-}6'H/C\text{-}2'H}$ = 1.6 Hz, C-6'H), 5.98 (2H, s, OCH_2O), 3.59 (1H, sext. $^3J_{CH/CH3} \approx {}^3J_{CH/CHA} \approx {}^3J_{CH/CHB}$ = 6.8 Hz, CH), 2.91 (1H, dd, $^2J_{gem}$ = 12.7 Hz, $^3J_{CHA/CH}$ = 5.5 Hz, C$\underline{\text{HA}}$HB), 2.84 (1H, dd, $^2J_{gem}$ = 12.8 Hz, $^3J_{CHB/CH}$ = 6.2 Hz, CHAC$\underline{\text{HB}}$), 1.31 (3H, d, $^3J_{CH3/CH2}$ = 6.6 Hz, CH_3); δ_C (D_2O + TSP) 150.4 (C-3'), 149.2 (C-4'), 132.7 (C-1'), 125.6 (C-6'), 112.5 (C-2' or C-5'), 111.6 (C-2' or C-5'), 104.0 (OCH_2O), 52.0 (CH), 42.6 (CH_2), 20.3 (CH_3). Hydroxylamine HCl (**6b**) impurity (< 5%): δ_H (D_2O + TSP) 5.97 (s, OCH_2O); MS(CI): 180 (100%, $[M+H]^+$, MDA **6a**), 196 (2%, $[M+H]^+$ **6b**).

1-(3',4'-Methylenedioxyphenyl)butan-2-amine HCl (**4c**) [7]. 2-Nitro-1-(3',4'-methylenedioxyphenyl)but-1-ene (**3c**) (2.0 g, 9.04 mmol, 1 eq) in THF (40 ml) was added dropwise to a suspension of $LiAlH_4$ (2.06 g, 54.2 mmol, 6 eq) in THF (25 ml). The reaction mixture was heated at reflux for 22 h. Work-up as described for (**4b**). The crude oil was dissolved in DCM, saturated with anhydrous HCl for 30 min and concentrated to give beige crystals of (**4c**) (771 mg, 3.36 mmol, 37.2%). Mp 152-154°C, Lit mp 159-161°C [7]; δ_H (D_2O + TSP) 7.01-6.76 (3H, m, CH aromatic), 5.98 (2H, s, OCH_2O), 3.49-3.39 (1H, m, CH), 3.00 (1H, dd, $^2J_{gem}$ 14.3 Hz, $^3J_{CHA/CH}$ 6.0 Hz, C$\underline{\text{HA}}$CHB), 2.79 (1H, dd, $^2J_{gem}$ 14.3 Hz, $^3J_{CHB/CH}$ 8.3 Hz, CHAC$\underline{\text{HB}}$), 1.82-1.59 (2H, m, CH_2 (chain)), 1.03 (3H, t, $^{3}J_{CH3/CH2(chain)}$ 7.5 Hz, CH_3); δ_C (D_2O + TSP) 150.4 (C-3'), 149.2 (C-4'), 132.6 (C-1'), 125.6 (C-6'), 112.5 (C-2' or C-5'), 111.6 (C-2' or C-5'), 104.0 (OCH_2O), 57.4 (CH), 40.3 (CH_2), 27.8 ($CH_{2(chain)}$), 11.7 (CH_3). Hydroxylamine HCl (**6c**) trace impurity: δ_H (D_2O + TSP) 6.00 (s, OCH_2O), 0.93 (t, J 7.6 Hz, CH_3). MS(CI): 194 (100%, $[M+H]^+$, BDB **4c**), 210 (2%, $[M+H]^+$ **6c**).

2,5-Dimethoxyamphetamine HCl (**4d**) and (+/-)-1-(2',5'-dimethoxyphenyl)propan-2-hydroxylamine HCl impurity (**6d**) were prepared by the method of Shulgin and Shulgin [7]. 2-Nitro-1-(2',5'-dimethoxyphenyl)prop-1-ene (**3d**) (0.5 g, 2.24 mmol, 1 eq) in THF (15 ml) was added dropwise to $LiAlH_4$ (0.34 g, 8.96 mmol, 4 eq) in THF (20 ml). The reaction mixture was heated at reflux overnight. After cooling, water and NaOH (15%) were added until the pH > 9.0. The reaction mixture was evaporated and then water and DCM were added. The pH was adjusted to 2.0 by the addition of HCl (20%), and the aqueous layer collected. The solution was made basic (aq. NaOH), re-extracted into DCM and dried ($MgSO_4$). The solution was reduced to brown oil which was dissolved in propan-2-ol, acidified (HCl conc.) and diethyl ether was added. The solution was evaporated to give a yellow solid (87.0 mg, 0.38 mmol, 17%). ^{1}H NMR showed a mixture of DMA HCl (**4d**) (82%) and 1-(2',5'-dimethoxyphenyl)propan-2-hydroxylamine HCl (**6d**) (18%). MS(CI): 212 (10%, $[M+H]^+$ **6d**), 196 (100%, $[M+H]^+$, DMA **4d**); δ_H (D_2O, benzene) DMA HCl 6.90-6.70 (3H, m, C-3'H, C-4'H, C-6'H), 3.66 (3H, s, OMe), 3.64 (3H, s, OMe), 3.49 (1H, ddq ≈ sext, $^{3}J_{CH/CH3} \approx {}^{3}J_{CH/CHA} \approx {}^{3}J_{CH/CHB} = 6.8$ Hz, CH), 2.79 (1H, dd, $^{2}J_{gem}$ 13.9 Hz, $^{3}J_{CHA/CH}$ 7.2 Hz, C$\underline{\text{HA}}$CHB), 2.73 (1H, dd, $^{2}J_{gem}$ 13.9 Hz, $^{3}J_{CHB/CH}$ 7.2 Hz, CHAC$\underline{\text{HB}}$), 1.14 (3H, d, $^{3}J_{CH3/CH}$ 6.6 Hz, CH_3); δ_C (D_2O, benzene) DMA HCl: 152.7 (C-5'), 151.9 (C-2'), 117.6 (C-3'H), 125.3 (C-1'), 113.5 (C-6'H), 112.7 (C-4'H), 55.9 (OMe), 55.8 (OMe), 48.2 (CH), 34.9 (CH_2), 17.6 (CH_3). Hydroxylamine HCl impurity (**6d**): δ_H (D_2O, benzene) include 2.91 (dd, $^{2}J_{gem}$ 13.9 Hz, $^{3}J_{CHA/CH}$ = 6.4 Hz, C$\underline{\text{HA}}$CHB), 1.03 (d, $^{3}J_{CH3/CH}$ 6.8 Hz, CH_3), other peaks overlapping with DMA HCl **4d**.

2,5-Dimethoxyamphetamine HCl (**4d**) was prepared by the method described by Butterick and Unrau [18]. 2-Nitro-1-(2',5'-dimethoxyphenyl)prop-1-ene (**3d**) (0.25 g, 1.12 mmol, 1 eq) in toluene (5ml) was added dropwise to Red-Al (65% in toluene) (3.14 g, 10.1 mmol, 9 eq). The reaction mixture was then heated at reflux for 17 h to give a colourless solution. Water was added and the resulting white precipitate was removed by filtration, washed with toluene and discarded. The toluene solution was evaporated to a pale brown liquid (109 mg). The liquid was dissolved in diethyl ether and HCl(g) was bubbled though the solution for 20 min. The acidified solution was then evaporated to give brown oil (114 mg, 0.49 mmol, 43.9%). TLC (100:1.5; MeOH/NH_3) R_f = 0.77, 0.42 (TMA), Lit R_f = 0.37 (DMA) [19]. (NMR data as previously stated). 1-(2',5'-Hydroxylamine trace impurity (**6d**): δ_H (D_2O + benzene) peaks include: 1.01 (d, $^{3}J_{CH3/CH}$ = 6.9 Hz, CH_3), other peaks overlapping.

2-Nitro-1-(2',5'-dimethoxyphenyl)propane (**5d**) was produced by the method of Hutchins and co-workers [20]. A slurry of 2-nitro-1-(2',5'-dimethoxyphenyl)prop-1-ene (**3d**) (0.5 g, 2.24 mmol, 1 eq), sodium cyanoborohydride (155 mg, 2.46 mmol, 1.1 eq) and absolute ethanol (6 ml) was stirred. A small amount of bromocresol green was added and a yellow solution resulted. HCl (conc.) was added to keep the colour of the reaction mixture yellow, with the pH stabilised after 1 h. The reaction mixture was left stirring overnight. Further sodium cyanoborohydride (155 mg, 2.46 mmol, 1.1 eq) was added and the reaction mixture was stirred for 2 h. Water (35 ml) was added and the product was extracted into diethyl ether and washed with basified water. The organic solution was dried and evaporated (216 mg, 0.85 mmol, 38%). Column chromatography (3:1, hexane-ethyl acetate, 1% TEA) gave (**5d**) as a yellow oil (47.8 mg, 0.19 mmol, 8.4%). TLC (3:1; hexane-ethyl acetate, 1% TEA) R_f 0.54. δ_H ($CDCl_3$) 6.80-6.60 (3H, m, C-3'H, C-6'H and C-4'H), 4.91 (1H, ddq ≈ sext, $^{3}J_{CH/CHA} \approx {}^{3}J_{CH/CHB} \approx {}^{3}J_{CH/CH3} \approx 6.8$ Hz, CH), 3.79 (3H, s, OMe), 3.74 (3H, s, OMe), 3.23 (1H, dd, $^{2}J_{gem}$ 13.6 Hz, $^{3}J_{CHA/CH}$ 7.7 Hz, C$\underline{\text{HA}}$CHB), 3.02 (1H, dd, $^{2}J_{gem}$ 13.6 Hz, $^{3}J_{CHB/CH}$ 6.5 Hz, CHAC$\underline{\text{HB}}$), 1.53 (3H, d, $^{3}J_{CH3/CH}$ 6.7 Hz, CH_3); δ_C ($CDCl_3$) 153.3 (C-5'), 151.6 (C-2'), 124.9 (C-1'), 117.3 (C-3'), 112.8 (C-6'), 111.1 (C-4'), 82.8 (CH), 55.7 (C-2'OMe or C-5'OMe), 55.7 (C-2'OMe or C-5'OMe), 36.6 (CH_2), 19.1 (CH_3).

1-(3',4',5'-Trimethoxyphenyl)propan-2-hydroxylamine HCl (**6e**) [21]. $NaBH_4$ (236 mg, 6.23 mmol, 3.2 eq) and BF_3-Et_2O (1.22 g, 7.91 mmol, 4 eq) in THF (10 ml) were stirred at 0°C for 10 min. The ice bath was then removed and the mixture was left to reach room temperature over 20 min. 2-Nitro-1-(3',4',5'-trimethoxyphenyl)prop-1-ene (**3e**) (0.5 g, 1.98 mmol, 1 eq) in THF (8 ml) was then added dropwise and the reaction mixture was stirred at room temperature for 5 h. Ice was added and THF was removed by evaporation. HCl 1M (20 ml) was added and the reaction mixture was heated at 80-85°C for 2h. Method continued as described for (**4a**). After 48 h in the fridge crystals were formed and filtration produced beige crystals of (**6e**) (51 mg, 0.18 mmol, 9.3%): δ_H (D_2O + benzene) 6.52 (2H, s, C-2'H and C-6'H), 3.71 (6H, s, C-3'O$\underline{CH_3}$ and C-5'O$\underline{CH_3}$), 3.61 (3H, s, C-4'$\underline{OCH_3}$), 3.67 –3.57 (1H, m, CH), 2.97 (1H, dd, $^{2}J_{gem}$ = 13.7 Hz, $^{3}J_{CHA/CH}$ = 5.9 Hz, C$\underline{\text{HA}}$CHB), 2.67 (1H, dd, $^{2}J_{gem}$ = 13.7 Hz, $^{3}J_{CHB/CH}$ = 8.4 Hz, CHAC$\underline{\text{HB}}$), 1.13 (3H, d, $^{3}J_{CH3/CH}$ = 6.6 Hz,

CH_3); δ_C (D_2O + benzene): 152.6 (C-3' and C-5'), 135.7 (C-4'), 132.5 (C-1'), 106.8 (C-2' and C-6'), 60.9 (CH or C-4'O$\underline{CH_3}$), 58.7 (CH or C-4'O$\underline{CH_3}$), 56.0 (C-3'O$\underline{CH_3}$ and C-5'O$\underline{CH_3}$), 36.4 (CH_2), 13.4 (CH_3); MS(CI): 242 (65%, MH^+), 224 (30%), 209 (18%), 183 (17%); GC-MS (B) t_R = 23.9 min. (EI) 182 (52%), 167 (16%); GC-MS (B): t_R 29.8 min. (EI): 239 (22%, $M^{\bullet+}$), 224 (11%), 208 (32%), 206 (11%), 181 (36%), 167 (100%).

3,4,5-Trimethoxyamphetamine HCl (**4e**) and 1-(3',4',5'-trimethoxyphenyl)propan-2-hydroxylamine HCl (**6e**) impurity were prepared by the method described by Shulgin and Shulgin [7]. 2-Nitro-1-(3',4',5'-trimethoxyphenyl)prop-1-ene (**3e**) (2.0 g, 7.90 mmol, 1 eq) in diethyl ether (15 ml) was added dropwise to $LiAlH_4$ (0.6 g, 15.8 mmol, 2 eq) in diethyl ether (20 ml). The reaction mixture was then heated at reflux overnight. After cooling, water was added to destroy the excess $LiAlH_4$ and the white solid produced was filtered off and washed with diethyl ether. The method continued as described for the synthesis of (**4b**) except diethyl ether was used as the extraction solvent in place of DCM. Pale pink crystals (84.7 mg) were collected by filtration following 24 h in the fridge. The crystals were a mixture of (**4e**) (81%) and (**6e**) (19%). TLC: (100:1.5; MeOH/NH_3 developed with ninhydrin) R_f 0.69 (**6e**), 0.38 (TMA **4b**); Lit R_f 0.35 [19]; δ_H (D_2O + benzene) TMA: 6.50 (1H, s, C-2'H), 6.49 (1H, s, C-6'H), 3.71 (6H, s, C-3'O$\underline{CH_3}$ and C-5'O$\underline{CH_3}$), 3.61 (3H, s, C-4'$\underline{OCH_3}$), 3.49 (1H, m, CH), 2.73 (2H, d, $^3J_{CH2/CH}$ = 7.2 Hz, CH_2), 1.17 (3H, d, $^3J_{CH3/CH}$ = 6.6 Hz, CH_3). Hydroxylamine HCl (**6e**) impurity: Analytical data as previously stated.

(+/-)-2,4,5-Trimethoxyamphetamine HCl (**4f**). 2-Nitro-1-(2',4',5'-trimethoxyphenyl)prop-1-ene (**3f**) was reduced using Red-Al in toluene as described for DMA (**4d**) with the exception that the reaction mixture was heated at reflux for 4 h. TLC: (100:1.5; MeOH/NH_3) R_f 0.29 (product). TMA-2 free base was produced as a brown liquid (260 mg, 1.15 mmol, 58.5%). TMA-2 HCl was produced as a brown solid (247 mg, 0.94 mmol, 47.9%). δ_H (D_2O + benzene) 6.50 (1H, s, C-3'H or C-6'H), 6.34 (1H, s, C-3'H or C-6'H), 3.51 (3H, s, OMe), 3.48 (3H, s, OMe), 3.45 (3H, s, OMe), 3.30-3.18 (1H, ddq ≈ sext, $^3J_{CH/CH2} \approx {}^3J_{CH/CH3} \approx$ 6.9 Hz, CH), 2.56-2.41 (2H, d, $^3J_{CH2/CH}$ 6.9 Hz, CH_2), 0.96 (3H, d, $^3J_{CH3/CH}$ 6.6 Hz, CH_3); δ_C (D_2O + benzene): 151.9 (C-2'), 148.2 (C-4'), 141.9 (C-5'), 115.5 (C-1'), 115.3 (C-6'), 98.0 (C-3'), 56.3 (OMe), 56.2 (OMe), 55.9 (OMe), 48.5 (CH), 34.3 (CH_2), 17.6 (CH_3); MS(CI): 226 (100%, $[M+H]^+$), 209 (30%), 182 (39%).

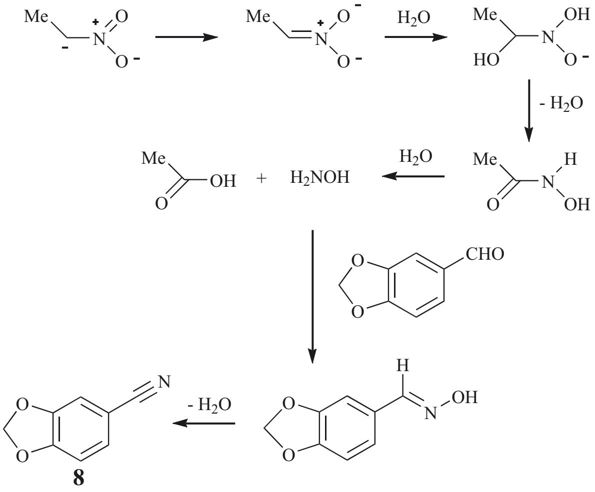

Figure 2. Proposed route for the formation of 3,4-methylenedioxybenzonitrile (**8**). This by-product only occurred during the preparation of nitrostyrenes (**3b**) and (**3c**) where glacial acetic acid was used as the solvent.

3. Results and Discussion

The Henry reaction is versatile and can be used to prepare a wide range of nitrostyrenes (e.g. **3a-3f**) by using the appropriate nitroalkane (e.g. R' = Me, Et) and base and aryl aldehyde (**1a-1f**). However, during the synthesis of 2-nitro-1-(3',4'-methylenedioxyphenyl) prop-1-ene (**3b**) from piperonal and nitroethane in the presence of glacial acetic acid and ammonium acetate [13] only a small amount of nitrostyrene was detected by ^1H NMR spectroscopy. An impurity was isolated in 5.6% yield and subsequently characterised as 3,4-methylenedioxybenzonitrile (**8**) (Fig. 2).

A standard of this nitrile (**8**) was synthesised by heating hydroxylamine with piperonal in the presence of ammonium acetate and glacial acetic acid. The analytical data obtained were identical to the reaction impurity isolated, of note being the IR stretch at 2220 cm^{-1} and the ^{13}C NMR peak at 105.0 ppm for the CN group [22]. Fig. 2 shows a proposed mechanism for the formation of nitrile (**8**) that first requires the formation of hydroxylamine [14,15,23].

If the presence of this arylnitrile impurity was route-specific, then its detection would allow the forensic chemist to identify the nitrostyrene route. Furthermore, it seems conceivable that nitrile (**8**) would also be carried through to the subsequent reduction step, the final phenylalkylamine would therefore be expected to contain the corresponding amine $ArCH_2NH_2$. The extent of this reduction however, may depend on the reducing agent employed. Khurana and Kukreja have shown that nitrile (**8**) could be reduced to the primary amine using $NaBH_4$ in the presence of nickel(II) boride, however

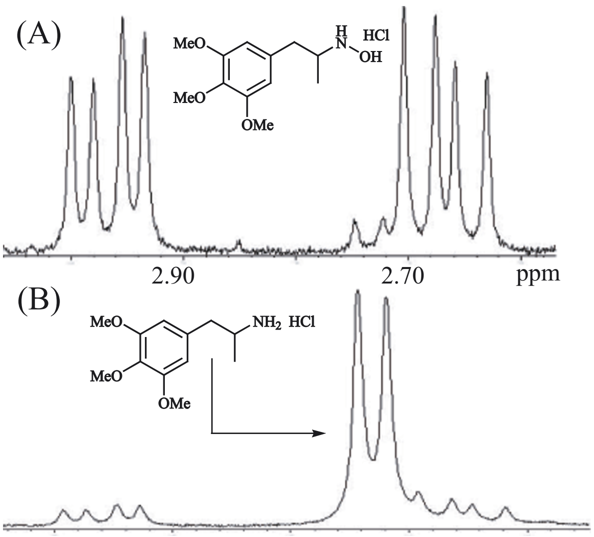

Figure 3. **(A)** Partial ^{1}H NMR spectrum of the nitrostyrene (**3e**) reduction products using BH_3 at reflux. Major product was 1-(3',4',5'-trimethoxyphenyl)propan-2-hydroxylamine HCl (**6e**). The minor product was TMA HCl (**4e**) which was detected in the crude product. **(B)** Nitrostyrene (**3e**) reduction products using LiAlH4 at reflux. Major product was TMA HCl (**4e**). Approximately 19% hydroxylamine (**6e**) was detected.

under these conditions, 5% of the corresponding dimeric product $(ArCH_2)_2NH$ has also been identified [24]. $LiAlH_4$ has also been shown to be an effective reducing agent for the nitrile [25].

The impact of nitrile (**8**) or any of the reduced derivatives on human health is currently unknown. On the other hand, the amphetamine counterpart benzonitrile is known to be toxic if orally absorbed, causing irritation to the gastrointestinal tract leading to nausea, vomiting and even cyanide poisoning. It appears conceivable to expect that 3,4-methylenedioxybenzonitrile (**8**) may also be toxic, and therefore it is important to have methods for its identification and an appreciation of the reaction conditions for its formation.

3,4-Methylenedioxybenzonitrile (**8**) formation indicated that glacial acetic acid should not be used as the solvent in the Henry reaction. Thus, 2-nitro-1-(3',4'-methylenedioxyphenyl)prop-1-ene (**3b**) and its chain extended but-1-ene analogue (**3c**) were readily prepared by the reaction of piperonal with nitroethane or nitropropane as the solvent. Nitrostyrenes could be formed as two geometrical isomers, however for the synthesis of (**3b**), TLC and ^{1}H NMR spectroscopy indicated the presence of the most stable (*E*)-geometrical isomer only. Interestingly, in the case of the chain extended analogue 2-nitro-1-(3',4'-methylenedioxyphenyl)but-1-ene (**3c**), two geometrical isomers were observed by NMR spectroscopy and GC, with 3% of the minor (*Z*)-isomer being present. NOESY NMR gave an interaction between ring proton at position 2 and the methylene chain protons, confirming that the major isomer was indeed of the (*E*)-configuration. GC-MS analysis revealed that the minor (*Z*)-isomer eluted 0.4 min earlier than the (*E*)-isomer and gave complete baseline resolution. Both CI and EI mass spectra differed only slightly in intensity when both isomers were compared. A significant difference however, was apparent after the application of the CI tandem MS where a differentiation was possible. In case of the minor (*Z*)-isomer, $[M+H]^+$ disappeared completely and led to the base peak formation at m/z 151, in contrast to the major isomer where the protonated molecule at m/z 222 displayed a relative abundance of 70%.

3.1. Reduction of nitrostyrenes

Reduction of nitrostyrenes can form a range of compounds, including the phenylalkylamines as shown in Fig. 1(A and B). The use of metal hydride reagents is common for the reduction of nitrostyrenes and metal borohydrides reduce the nitrostyrene to the nitroalkane, leaving the nitro group intact [26]. The reduction of the nitro group is known to be stepwise, producing nitroso (RNO), then hydroxylamine (RNHOH) before forming the amine [27].

Reduction of 2-nitro-1-(3',4',5'-trimethoxyphenyl) prop-1-ene (**3e**) using BH_3 at room temperature resulted in the hydroxylamine (**6e**). This result was consistent with Kabalka and co-workers who reduced a selection of substituted nitrostyrene derivatives [21]. It has previously been shown that $NaBH_4$-catalysed reduction of nitroalkene derivatives by borane yielded the phenylalkylamine products after a 5.5 h reflux [16]. The preparation of 1-(3',4',5'-trimethoxyphenyl) propan-2-amine (**4e**, TMA) was attempted using this particular procedure, however only 5% of the desired amine was obtained. The product was predominantly 1-(3',4',5'-trimethoxyphenyl)prop-2-hydroxylamine (**6e**) (95%). Fig. 3 shows the partial ^{1}H NMR spectrum for the reduction product mixture. The protons for the methylene group in (**6e**) are non-equivalent due to the presence of the chiral C and N centres, and are shown as a pair of dd with an AX pattern (Fig. 3(A)). In contrast, the methylene group of TMA (**4e**) was observed as a doublet, as indicated in Fig. 3(B).

When the BH_3 reduction was repeated with 2-nitro-1-phenyl-prop-1-ene (**3a**) (heating at reflux for 3 hours), 80% of the product was amphetamine (**4a**), with the formation of 20% 1-phenyl-propan-2-hydroxylamine (**6a**). BH_3 reduction was found to give some hydroxylamine and complete reduction to the phenylalkylamine appeared to be substrate-dependent. Fig. 1(B) indicates that when 2-nitro-1-(2',5'-dimethoxyphenyl)prop-1-ene (**3d**) was reduced with $NaBH_3CN$ the nitroalkane 2-nitro-1-(2',5'-

dimethoxyphenyl)propane (**5d**) was formed. The point to make with this particular example is that access to desired reducing agents may not always be possible in a clandestine situation. Consequently, it appears likely that incompletely reduced nitroalkane derivatives may be present under certain reducing conditions.

Hydroxylamine is a product of partial reduction of the nitro group therefore a stronger reducing agent might be predicted to completely reduce the nitrostyrene to the phenylalkylamine. However, when $LiAlH_4$ was employed, examination of the crude ^1H NMR spectrum revealed the presence of up to 20% of the hydroxylamine impurity. A representative example is shown in Fig. 3 where reduction of 2-nitro-1-(3',4',5'-trimethoxyphenyl)prop-1-ene (**3e**) with $LiAlH_4$, gave 81% TMA (**4e**) together with 19% hydroxylamine (**6e**), Fig. 3(B). $LiAlH_4$ reduction of 2-nitro-1-(2',5'-dimethoxyphenyl)prop-2-ene (**3d**) gave largely DMA (**4d**) with 18% of 1-(2',5'-dimethoxyphenyl) propan-2-hydroxylamine (**6d**). In contrast to TMA (**4e**), the ^1H NMR of the methylene group of DMA was observed as a pair of dd with an AB pattern. The reductions of 2-nitro-1-(3',4'-methylenedioxyphenyl)prop-1-ene (**3b**) and its but-1-ene analogue (**3c**) with $LiAlH_4$ gave MDA (**4b**) and BDB (**4c**), respectively, with only traces of the hydroxylamines (**6b**) and (**6c**) apparent by ^1H NMR spectroscopy.

The use of sodium bis(2-methoxyethoxy) aluminium dihydride (Red-Al) has been proposed by Butterick and Unrau where some nitrostyrenes have been completely reduced [18]. The reduction of 2-nitro-1-(2',5'-dimethoxyphenyl)prop-2-ene (**3d**) and 2-nitro-1-(2',4',5'-trimethoxyphenyl)prop-1-ene (**3f**) to DMA (**4d**) and TMA-2 (**4f**), respectively, proceeded smoothly without any evidence for the formation of hydroxylamines (**6d**) and (**6f**). This indicated that Red-Al was a good substitute for $LiAlH_4$ which allowed for easier and safer handling due to its lack of pyrophoric properties in solution. Red-Al may be the method of choice for the application to a larger group of nitrostyrenes.

3.2. MS analysis of 1-phenylpropan-2-hydroxylamines

In a forensic context where fingerprinting analysis is desired, the nature of the sample may preclude NMR analysis, particularly if only small amounts are present. In such a case GC-MS analysis is often employed as a powerful technique for the detection and identification of trace impurities. The hydroxylamine impurities, which had been identified by ^1H NMR spectroscopy, were analysed by GC-MS. Exposure of hydroxylamines **6a-6f** to heat in the injection port resulted in the conversion to the corresponding oxime derivatives **7a-7f** as illustrated by a representative example in Fig. 1(C). This phenomenon occurred to a different degree and was detectable by the presence of an additional peak in the total ion chromatogram at different retention times. When the softer electrospray ionisation MS was used no such derivative could be detected which provided additional support for the artificial formation of **7a**-**7f** due to the presence of heat during sample injection.

This observation was consistent with previous reports on similar derivatives and mechanistically this was ascribed to pyrolytic disproportionation. Indeed, Dal Cason has also shown that 1-(3',4'-methylenendioxyphenyl) propan-2-hydroxylamine (**6b**) was difficult to characterise by GC-MS which resulted in the detection of 1-(3',4'-methylenendioxyphenyl)propan-2-oxime (**7b**) and concomitant reduction of a second molecule to MDA (**4b**) [28]. The same thermal degradation has been documented by Beckett and co-workers when primary phenylethylhydroxylamines were exposed to hot injection [29]. Also, thermal decomposition of 1-(3',4'-methylenedioxyphenyl)butan-2-hydroxylamine was reported to give six rearrangement products (including oxime and amine) under GC-MS conditions [30]. Product stabilities are structure-dependent: for example, hydroxylamine (**6a**) showed complete disproportionation, whereas 1-(3',4',5',-trimethoxyphenyl)propan-2-hydroxylamine (**5d**) was thermally more stable under GC-MS conditions (not shown).

4. Conclusion

The nitrostyrene route utilising the Henry reaction is a simple procedure used to prepare racemic psychoactive phenylalkylamines drugs, which also makes it a popular method within the clandestine and medicinal chemistry communities. The analytical data presented here for key nitrostyrenes, phenylalkylamines, nitrile and hydroxylamines are aimed to contribute to the database of information on intermediates and impurities in clandestine drug preparations. The toxicological implications of these by-products remain to be investigated.

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