Convenient and Efficient Syntheses of 4-Hydroxy-2(*E*)-nonenal and 4-Oxo-2(*E*)-nonenal

Reshma F. Kurangi[a], Santosh G. Tilve[a], and Ian A. Blair[b]

[a]Department of Chemistry, Goa University, Taliegao Plateau, Goa, India, and [b]Center for Cancer Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6160, USA

ABSTRACT: Lipid peroxidation products 4-hydroxy-2(*E*)-nonenal (HNE) and 4-oxo-2(*E*)-nonenal (ONE) were conveniently synthesized using Wittig and Horner-Wardsworth-Emmons (HWE) reaction. Wittig or HWE reaction between an easily prepared phosphorane or phosphonate with glyoxal dimethyl acetal gave a protected 4-oxo-2(*E*)-nonenal. Hydrolysis gave 4-oxo-2(*E*)-nonenal, whereas reduction followed by hydrolysis gave 4-hydroxy-2(*E*)-nonenal.

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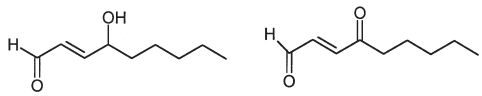
Lipid peroxidation in biological systems produce many degradation products including 4-hydroxy-2(*E*)-nonenal (HNE) **1** and 4-oxo-2(*E*)-nonenal (ONE) **2** (1,2). These are well known for their genotoxic and cytotoxic effects (1,3–5). The extreme cytotoxicity of HNE is a manifestation of its ability to inhibit several enzymes like protein kinase C, adenylate cyclase, glyceraldehyde-3-phosphate dehydrogenase, and others through modification of nucleophilic amino acid residues (6–9). HNE has been shown to induce apoptosis (10,11) and to cause changes in global gene expression (12). HNE readily modifies nucleophilic protein side chains and DNA bases and its bifunctionality results in protein cross-linking (13,14).



1 **2**

There is increasing evidence that HNE is casually involved in most of the pathophysiological effects associated with inflammatory and oxidative stress in cells and tissues (15,16). HNE is thought to play a significant role in neurodegenerative diseases, in particular Alzheimer's disease (17–20) and Parkinson's disease (21–23). In addition to studies on its toxicity, protein and DNA adducts of HNE are commonly used as a biomarker for the occurrence and/or the extent of lipid peroxidation (24).

ONE is an even more potent electrophile and therefore more neurotoxic and highly protein reactive (5). Thus, both HNE and ONE participate in the formation of DNA adducts, making it possible to assess the role of lipid peroxidation in mutagenesis and carcinogenesis (2).

We required substantial amounts of these compounds for our study. Previous procedures for HNE preparation employed variations in the Grignard reaction (25–30), isomerization of 2-yne-1,4-diols with ruthenium catalyst (31), a method via 1,3-bis(methylthio)allyl-lithium (32), a sequence of addition/elimination/substitution reaction performed on the corresponding saturated aldehyde (33,34), epoxidation of 3(*Z*)-nonenol, oxidation, and isomerization (35). A method for chiral synthesis for HNE is also reported (36) which involves Sharpless epoxidation, reaction with an unstable Wittig reagent followed by isomerization (36). The methods for the synthesis of ONE employed lithiation of furan using *n*-BuLi, alkylation using *n*-pentyliodide, followed by either methoxylation using bromine in methanol, ring cleavage and isomerization (37), or oxidative ring opening of furan using PCC (38). We report herein a simple and convenient method for the preparation of HNE **1** and ONE **2.**

EXPERIMENTAL PROCEDURES

^{1}H NMR and ^{13}C NMR spectra were recorded on 300-MHz and 400-MHz Bruker instruments. The multiplicities of carbon signals were obtained from a distortionless enhancement by polarization transfer (DEPT) experiment. Chemical shifts (ppm) are relative to the internal standard Me_4Si (0 ppm). IR spectra were recorded on a Shimadzu FT-IR spectrophotometer (KBr pellet or neat sample). TLC was performed on silica gel G (13% $CaSO_4$ as binder). Triethylphosphonoacetate was purchased from Aldrich Chemical Company (Sigma-Aldrich, Mumbai, India), and Glyoxal dimethyl acetal was purchased from Lancaster (Lancaster, A Clariant Group Company, Chennai, India).

The stable Wittig reagent ethyl (triphenylphosphoranyliden)acetate **3a** was acylated with hexanoyl chloride to provide acylated Wittig reagent **4a** (39). The Wittig reagent **4a** on decarboxylative hydrolysis provided acyl Wittig reagent 1-(triphenylphosphoranylidene)-2-heptanone **5a** (Scheme 1).

The diethyl-2-oxoheptylphosphonate **5b** was prepared by acylating triethyl phosphonoacetate to obtain **4b**. Hydrolysis and decarboxylation of **4b** gave phosphonate **5b** (Scheme 2).

On condensation of **5a** or the anion of phosphonate **5b** with glyoxal dimethyl acetal, an α,β-unsaturated ketone **6** was formed, which on deprotection gave ONE **2** and after reduction followed by deprotection gave HNE **1** (Scheme 3).

*To whom the correspondence should be addressed at Department of Chemistry, Goa University, Taleigao Plateau, Goa, India 403206.
E-mail: santoshtilve@yahoo.com

Abbreviations: DEPT, distortionless enhancement by polarization transfer; HNE, 4-hydroxy-2(*E*)-nonenal; ONE, 4-oxo-2(*E*)-nonenal.

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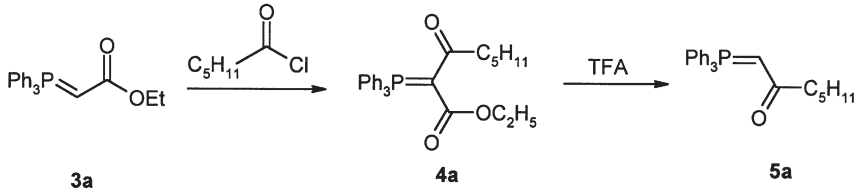
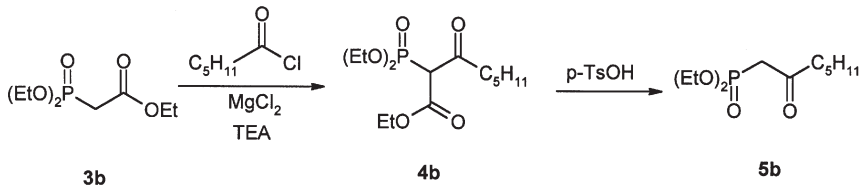


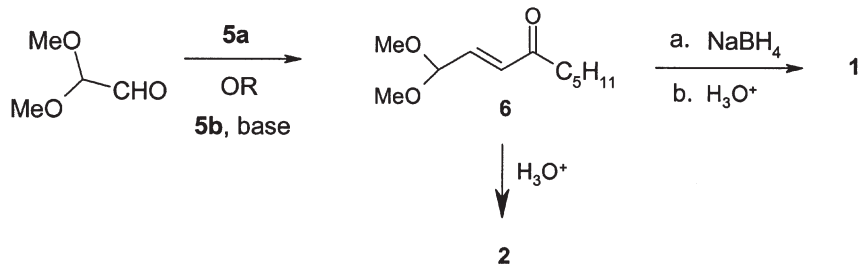
3a **4a** **5a**

SCHEME 1



3b **4b** **5b**

SCHEME 2



SCHEME 3

*Preparation of Wittig reagent (**5a**).* The stable Wittig reagent **3a**, 5.2 g (14.8 mmol), dissolved in toluene (15 mL) was added to hexanoyl chloride 1 g (7.4 mmol). The yellow solid obtained, after stirring for 5.0 h at room temperature, was filtered. The product obtained after concentration of the filtrate under reduced pressure was 3.1 g (**4a**, yield 93.5%). IR (KBr): ν_{max} 2949.16, 2927.94, 2850.00, 1662.64, 1556.55, 1103.28, 752.20, 692.40 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ_{ppm} 0.63 (t, 3H, J = 7.1 Hz, CH_3), 0.83 (t, 3H, J = 6.8 Hz, CH_3), 1.28 (m, 4H, CH_2), 1.59 (m, 2H, CH_2), 2.84 (t, 2H, J = 7.6 Hz, CH_2CO), 3.70 (q, 2H, J = 7.1 Hz, CH_2), 7.40–7.65 (m, 15H, ArH). A solution containing 1.70 g (3.8 mmol) of phosphorane **4a** in a mixture of trifluoroacetic acid (15 mL) and water (2.5 mL) was heated under reflux for 6.0 h. The reaction mixture was then poured onto ice and basified with 2% sodium bicarbonate solution. This was followed by extraction with diethyl ether (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexanes (1:5 vol/vol) to obtain 0.71 g (yield 50%) of **5a**. IR (KBr): ν_{max} 2927.56, 1537.25, 1436.00, 1392.31, 1195.14, 751.21, 749.51, 719.45 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ_{ppm} 0.80 (t, 3H, J = 7.0 Hz, CH_3), 1.25 (m, 4H, 2 × CH_2) 1.58 (m, 2H, CH_2), 2.22 (t, 2H, J = 7.1 Hz, CH_2CO), 4.37 (br s, 1H, $CH{=}PPh_3$), 7.2–7.6 (m, 15H, ArH).

*Preparation of **5b**.* A solution of hexanoyl chloride 5.8 g (43.12 mmol) in dry toluene (21 mL) was slowly added over a period of 2.0 h. to a cold solution (5°C) of triethyl phosphonoacetate (9.7 g, 43.12 mmol), $MgCl_2$ (4.1 g, 43.12 mmol), and triethylamine (13.06 g, 129.4 mmol) in toluene (125 mL). The reaction was stirred for 6.0 h at room temperature; the reaction was then quenched into an ice-cold solution of 10% H_2SO_4 (125 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were dried over Na_2SO_4. The product **4b** obtained after filtration and concentration of the organic layer was 13.3 g (yield 96.18%). The compound was judged as pure by observation of a single spot on TLC (ethyl acetate/hexanes 2:3 vol/vol). A solution of **4b** (13.3 g, 43.4 mmol) and *p*-toluenesulfonic acid (0.21 g, 1.2 mmol) in H_2O (175 mL) was heated under reflux for 3.0 h. The reaction mixture was extracted using diethyl ether (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4. The product obtained after filtration and solvent evaporation under reduced pressure was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:5 vol/vol) to obtain 8.1 g (yield 74.7%) of **5b**. IR (neat): ν_{max} 2958.00, 2932.00, 1708.04, 1254.75, 1025.21, 964.45 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ_{ppm} 0.81 (t, 3H, J = 6.9 Hz, CH_3), 1.20 (m, 4H, 2 × CH_2), 1.27 (t, 6H, J = 7.0 Hz, OCH_2CH_3), 1.52 (m, 2H, CH_2CH_2CO), 2.55 (t, 2H, J = 6.9 Hz,

CH_2CO), 3.00 (d, 2H, J = 22.8 Hz, $COCH_2P$), 4.06 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.11 (q, 2H, J = 7.0 Hz, OCH_2CH_3).

*Preparation of α,β-unsaturated ketone (**6**) from **5a.*** A solution containing glyoxal dimethyl acetal 4.0 g (10.7 mmol) and Wittig reagent **5a** 1.8 g (11.7 mmol) in methanol (20 mL) was heated at reflux for 3.0 h. The solvent was removed under reduced pressure and the residue was chromatographed (column chromatography, hexanes), giving 1.26 g (yield 59.03%) of **6** as an oil. IR (neat): ν_{max} 2956.87, 2933.73, 1709.00, 1680.00, 1130.29, 1058.92, 979.84 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_{ppm} 0.8 (t, 3H, J = 6.75 Hz, CH_3), 1.2 (m, 4H, 2 × CH_2), 1.56 (m, 2H, CH_2), 2.5 (t, 2H, J = 7.35 Hz, CH_2CO), 3.2 (s, 6H, OCH_3), 4.9 (d, 1H, J = 4.2 Hz, C*H*$(OCH_3)_2$), 6.3 (d, 1H, J = 16.2 Hz, =C*H*CO), 6.55 (dd, 1H, J = 16.2 & 4.2 Hz, CH=C*H*-CH). ^{13}C-NMR ($CDCl_3$) δ_{ppm} 14.20 (C9), 22.41 (C8), 23.71 (C7), 31.40 (C6), 40.65 (C5), 52.90 (C1), 101.10 (OCH_3), 132.10 (C2), 139.90 (C3), 200.46 (C4).

*Preparation of α,β-unsaturated ketone (**6**) from **5b.*** A solution of 1 g (25 mmol) of NaOH in 2 mL of H_2O was added to the mixture of 0.58 g (2.3 mmol) of **5b**, 0.35 g (3.3 mmol) of glyoxal dimethyl acetal, 0.04 g of tetrabutylammonium iodide in 3 mL of dichloromethane. After 30 min of stirring at 28°C, the reaction mixture was extracted with dichloromethane (3 × 5 mL). After drying all the combined organic layers over Na_2SO_4, filtration, and concentration, the resulting residue was passed through a silica gel column (hexanes) to obtain 0.43 g (yield 92.45%) of **6**.

*Preparation of **2.*** A solution containing α,β-unsaturated ketone **6** (0.1 g, 0.5 mmol) and citric acid (0.1 g) in water (10 mL) was stirred at room temperature for 2.0 h and then extracted in chloroform (3 × 10 mL). Combined organic extracts were concentrated to obtain 0.062 g (yield 80%) of the product. IR (neat): ν_{max} 2956.87, 2933.73, 2872.00, 1701.00, 1680.00, 1350.00, 1130.00, 1058.00 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_{ppm} 0.9 (t, 3H, J = 7.00 Hz, CH_3), 1.28 (m, 4H, 2 × CH_2) 1.61 (m, 2H, CH_2), 2.56 (t, 2H, J = 7.00 Hz, CH_2CO-), 6.35 (dd, 1H, J = 17.00 and 7.00 Hz, =CH-CHO), 6.6 (dd, 1H, J = 17.00, =CHCO), 9.78 (d, 1H, J = 7.00 Hz, CHO).

*Preparation of **2.*** To the stirred solution of **6** (0.1 g, 0.5 mmol) in dichloromethane (2 mL) was added 0.152 g of montmorillonite K-10 (40) and stirred at room temperature for 30 min. The reaction was filtered, the residue was washed with dichloromethane (2 × 5 mL), and the combined filtrate concentrated under vacuum to give 0.071 g (92%) of pure 4-ONE.

*Preparation of **1.*** Sodium borohydride 0.0208 g (0.55 mmol) was added to the solution of 0.1 g (0.5 mmol) of **6** in 5 mL absolute ethanol. After stirring the reaction for 2.0 h at 28°C, the solvent was removed under vacuum. To the residue, water (5 mL) was added and then extracted in diethyl ether (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain 0.097 g (96%) of the protected HNE. IR (neat): ν_{max} 3442.94 (br), 2931.80, 2858.51, 1130.29, 1053.13, 970.19 cm^{-1}.

To the stirred solution of the above protected HNE (0.0813 g, 0.4 mmol) in dichloromethane (2 mL) was added 0.123 g of montmorillonite K-10 and stirred at room temperature for 30 min. The reaction was filtered, the residue was washed with dichloromethane (2 × 5 mL), and the combined filtrate was concentrated under vacuum to give 0.064 g (83.5%) of pure HNE

IR (neat): ν_{max} 3442.94 (br), 2931.80, 2858.51, 1693.50, 975.98, 734.88. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_{ppm} 0.91 (t, 3H, J = 7.00 Hz, CH_3), 1.33 (m, 5H, 2 × CH_2 and C*H*CHOH), 1.65 (m, 2H, C*H*$_2$CH$_2$CHOH), 2.62 (t, 1H, J = 7.1 Hz, HC*H*CHOH), 4.45 (m, 1H, C*H*OH), 6.33 (m, 1H, CHOC*H*=), 6.84 (dd, 1H, J = 4.8, J = 15.6 Hz =C*H*CHOH), 9.6 (d, 1H, J = 7.1 Hz, CHO).

RESULTS AND DICUSSION

Previously described methods (25–38) mostly require anhydrous, inert, and/or cryogenic reaction conditions, use of organometallic reagent, and are used only for the preparation of either HNE or ONE. We required large amounts of both ONE and HNE for our studies so we visualized a convergent approach. The first approach using phosphorane gives us the key intermediate **6** in slightly low yield (59%) due to its decomposition on silica gel column. The latter phosphonate approach (Horner-Wardsworth-Emmons) was the most efficient method giving **6** in 92.5% yield. ONE was obtained from **6** using citric acid for hydrolysis in 74% overall yield. Use of montmorillonite K-10 (40) provided ONE in 83% overall yield. HNE was obtained from **6** by reduction with $NaBH_4$ followed by deprotection using montmorillonite K-10 in 80.7% overall yield. Both our methods are advantageous over the earlier methods in terms of overall yield, simplicity of procedures, availability of the chemicals, and also are easily scalable. In both methods the unsaturated ketone **6** has exclusive *E* geometry.

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