Synthesis of Δ^2-Isoxazoline Fatty Acid Ester Heterocycles

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ABSTRACT: Fatty ester Δ^2-isoxazoline heterocycles were prepared in good yields and excellent regioselectivity from 1,3-dipolar cycloaddition reactions between methyl 10-undecenoate and nitrile oxides. This methodology provides convenient access to the methyl esters of margaric (**4b**) and stearic (**4c**) acids in 63–66% yield that contain the isoxazoline heterocycle between C-10 and C-12. These fatty heterocycle compounds are synthesized in a one-pot sequence in which methyl 10-undecenoate is used to trap the reactive nitrile oxide intermediates that are generated by reacting aldoximes with aqueous sodium hypochlorite and a catalytic amount of triethylamine or by directly reacting hydroximic acid chlorides with a stoichiometric amount of base. The fatty ester Δ^2-isoxazoline heterocycles represent a versatile synthon that may be useful to obtain oleochemicals with potentially new and interesting properties not easily accessible by other methods.

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The 1,3-dipolar cycloaddition reaction between nitrile oxides and alkenes has been known for many years, and it provides convenient access to the complex five-membered heterocyclic ring system known as isoxazolines (1, an excellent review of nitrile oxide chemistry). Recently, interest in Δ^2-isoxazolines has increased markedly because of reports describing their pharmacological properties (2,3) and because Δ^2-isoxazolines represent a synthetically versatile intermediate that readily undergoes further transformations, e.g., alkylation (4), dehydrogenation to isoxazoles (5), or reductive cleavage to expose functionality such as β-hydroxy ketones, α,β-unsaturated ketones (6), or γ-amino alcohols (7).

Because nitrile oxides are highly reactive intermediates and dimerize readily to furoxans, they are usually generated *in situ* and trapped in the presence of olefinic substrates. The two most widely used routes to prepare isoxazolines by trapping nitrile oxides with alkenes are: (i) the Mukaiyama (8) method (or a variation thereof) in which primary nitroalkanes are reacted with a dehydrating agent such as aryl isocyanates and (ii) dehydrohalogenation of hydroximic acid chlorides obtained by reacting aldoximes with a halogenating agent such as *N*-chlorosuccinimide (9) or chlorine (10). The aldoxime route is a convenient method to generate nitrile oxides to be trapped by olefins, and recently a simple procedure was reported in which water-insoluble aldoximes are reacted with sodium hypochlorite (household bleach) under biphasic conditions (11). This methodology represents a practical entry into Δ^2-isoxazolines because the starting materials needed are generally inexpensive and readily available, and importantly, the simplicity of the reaction allows it to be readily scaled up.

The straightforward synthesis of Δ^2-isoxazolines from nitrile oxides and their potentially interesting properties coupled with their synthetic versatility make them an interesting class of compounds that have potential industrial or biological applications. Herein, we now report an initial study focused on the synthesis of long-chain fatty ester Δ^2-isoxazoline heterocycles made by reacting methyl 10-undecenoate with various nitrile oxides generated *in situ* from readily obtainable aldoxime or hydroximic acid chloride precursors.

EXPERIMENTAL PROCEDURES

Materials. Methyl 10-undecenoate was prepared by the esterification of 10-undecenoic acid (Kodak, Rochester, NY) in methanol using a catalytic amount of anhydrous HCl and was purified by Kugelrohr distillation (12). Acetaldoxime (**1a**) and *syn*-benzaldehyde oxime (**1e**) were purchased from Aldrich Chemical Co. (Milwaukee, WI). The oximes of hexanal (**1b**), heptanal (**1c**), octanal (**1d**), purchased from Lancaster Chemical Co. (Lancaster, PA), and trimethylacetaldehyde (**1f**), Aldrich Chemical Co., were prepared by the method of Bousquet (13). The oximes were recrystallized from ethanol/water and were dried *in vacuo* before use. Ethyl and methyl chlorooximidoacetates, **6g** and **6h**, were prepared according to the method reported by Kozikowski and Adamczyk (14). The materials were recrystallized from hexane dried under vacuum and used directly in the reactions. Sodium hypochlorite (10–15%) was purchased from Aldrich Chemical Co. Methylene chloride and chloroform were obtained from EM Science (Gibbstown, NJ). The chloroform was freshly distilled, to remove traces of H_2O, from anhydrous potassium carbonate before use. All other solvents were obtained from Fisher Scientific Co. (Fairlawn, NJ) and were used without further purification. Unless otherwise noted, all other chemicals were purchased from Aldrich Chemical Co. and were used without further purification.

Melting points. Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected.

Nuclear magnetic resonance (NMR). ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker ARX 400

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spectrometer (Billerica, MA) with a 5-mm dual proton/carbon probe (400 MHz ^{1}H/100.61 MHz ^{13}C) using $CDCl_3$ as the solvent in all experiments.

Fourier transform infrared. Infrared (IR) spectra were obtained using a PerkinElmer (Norwalk, CT) Spectrum RX FT-IR system as either a film on NaCl plates (liquids) or in a KBr matrix (solids).

Gas chromatography (GC). GC was performed with a Hewlett-Packard 5890 Series II gas chromatograph (Palo Alto, CA), equipped with a flame-ionization detector and an autosampler/injector. Analyses were conducted on an HP-5MS capillary column, 30 m × 0.25 mm i.d. (Hewlett-Packard). The column flow was 1.0 mL/min with helium head pressure of 15 psi (776 torrs); split ratio of 75:1; programmed ramp 100°C, for 2 min, ramp 100–210°C at 20°C/min, 210 to 250 at 10°C/min, hold 20 min at 250°C; injector and detector temperatures set at 280°C.

GC/mass spectrometry (MS). GC/MS analyses were conducted using a Hewlett-Packard 5890 Series II Plus GC [column: HP-5MS column (30 m × 0.25 mm i.d.); Hewlett-Packard Co.] coupled with a Hewlett-Packard 5989B mass spectrometer using a mass range of 50–550 amu. Electron ionization (EI) was performed at 70 eV, while positive chemical ionization (CI) used methane as reagent gas. GC conditions: helium head pressure 3 psi (155 torr); injector temperature set at 250°C; transfer line temperature set at 280°C; programmed ramp 100°C for 2 min, 100–210°C at 20°C/min, 210–270°C at 10°C/min, hold 20 min at 270°C.

Thin-layer and column chromatography. Analytical thin-layer chromatography was carried out on silica gel 60F254 (250 µm) purchased from Alltech Associates Inc. (Waukegan, IL). Conventional column chromatography was carried out using silica gel 22 (22–200 mesh) purchased from the Aldrich Chemical Co. The eluent used for analytical and preparative chromatography was 30:70 ethyl ether/hexane.

Determination of aqueous NaOCl concentration. The NaOCl solution used in the reactions was titrated for NaOCl concentration with a solution made from $Na_2S_2O_3{\cdot}5\ H_2O$ (20 g, 80.6 mmol) in 800 mL of deionized water (15). The $Na_2S_2O_3$ solution was standardized by titrating a solution of KIO_3 (102.8 mg, 0.48 mmol), KI (2 g, 12.0 mmol), 50% solution of H_2SO_4 (5 mL), and water (50 mL). When this purple solution turned yellow, 1% soluble starch solution (1 mL) was added, which reproduced a purple color. Additional $Na_2S_2O_3$ solution was added until the solution was clear. The concentration of the $Na_2S_2O_3$ solution was then calculated based on the volume of $Na_2S_2O_3$ added and the reaction of 1 mol of KIO_3 with 6 mol of $Na_2S_2O_3$. A solution of aqueous NaOCl (1 mL), KI (2 g, 12.0 mmol), 6 M HCl (2 mL), and deionized water was then titrated with the standardized $Na_2S_2O_3$ in the same manner as the KIO_3 titration. The NaOCl concentration was determined from the volume of $Na_2S_2O_3$ added and the reaction of 1 mol of NaOCl with 2 mol of $Na_2S_2O_3$. The aqueous NaOCl concentration (10–15% from Aldrich) was found to be 1.69 M (12.6%). The amount of aqueous NaOCl used in a reaction was determined based on its calculated concentration and the equivalents desired.

Representative procedure for the synthesis of Δ^2-isoxazolines from methyl 10-undecenoate and syn*-benzaldehyde oxime using sodium hypochlorite.* To a vigorously stirred mixture of methyl 10-undecenoate (3.51 g, 17.7 mmol), triethylamine (250 µL, 1.79 mmol), CH_2Cl_2 (20 mL), and aqueous sodium hypochlorite (12.6%, 19.0 mL, 38.6 mmol) at 2°C, a solution of benzaldehyde oxime (2.28 g; 18.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise (25 min) at a rate to maintain the temperature below 5°C. The mixture was stirred at <10°C for 2 h and then stirred at room temperature (rt) for an additional 2 h. The reaction phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 5.62 g of a light yellow solid (100%). One recrystallization from methanol gave 4.24 g of **4e** as white crystals (75%), m.p.: 59–60°C.

^{1}H NMR of 5-(9-methyl nonanoate)-3-phenyl-Δ^2-isoxazoline (**4e**): δ 7.70–7.66 (*m*, 2H, aromatic *H*), 7.44–7.40 (*m*, 3H, aromatic *H*), 4.75–4.72 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.68 (*s*, 3H, –OC*H*$_3$), 3.40 (*dd*, 1H, *J* = 16.4 and 10.3 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.98 (*dd*, 1H, *J* = 16.4 and 8.2 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.32 (*t*, 2H, *J* = 7.5 Hz, CH_2–C*H*$_2$–COOMe), 1.9–1.3 (*m*, 14H, alkyl chain *H*). ^{13}C NMR: δ 174.2 (*C*=O), 156.3 (*C*=N), 130.0 (aromatic *C*), 129.8 (aromatic *C*), 128.6 (aromatic *C*), 126.6 (aromatic *C*), 81.4 (CH_2–H*C*(O)–CH_2), 51.3 (O–*C*H$_3$), 39.9, 35.3, 34.1, 29.3, 29.3, 29.1, 29.0, 25.5, 24.9. IR (KBr) cm^{-1}: 2922, 2849, 1738, 1594, 1567. 5-(9-methyl nonanoate)-3-phenyl-Δ^2-isoxazoline GC retention time 20.2 min. MS (EI): *m/z* 317 (M^+, 1%), 286 ($M^+ - CH_3O$, 2%) and 146 (C_9H_8NO, 100%). MS (CI): *m/z* 318 (MH^+, 54%), 346 ($M^+ + C_2H_5$, 11%), 358 ($M^+ + C_3H_5$, 3%), 286 ($M^+ - CH_3O$, 16%), and 146 ($C_9H_8NO^+$, 4%).

The 5-(9-methyl nonanoate)-3-methyl-Δ^2- isoxazoline (**4a**) purified by column chromatography: ^{1}H NMR δ 4.55–4.45 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.64 (*s*, 3H, OC*H*$_3$), 2.94 (*dd*, 1H, *J* = 16.8 and 10.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.51 (*dd*, 1H, *J* = 16.9 and 8.2 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.27 (*t*, 2H, *J* = 7.5 Hz, CH_2–C*H*$_2$–COOMe), 1.95 (*s*, 3H, –CH_2–(N=)C–C*H*$_3$), 1.75–1.20 (*m*, 14H, alkyl chain H). ^{13}C NMR: δ 174.3 (*C*=O), 155.2 (*C*=N), 80.3 (CH_2–H*C*(O)–CH_2), 51.4 (O–*C*H$_3$), 43.7, 35.2, 34.0, 29.3, 29.2, 29.1, 29.0, 25.5, 24.9, 13.3. IR (NaCl) cm^{-1}: 2929, 2856, 1738 (C=O), 1632 (C=N). 5-(9-Methyl nonanoate)-3-methyl-Δ^2-isoxazoline GC retention time 11.3 min. MS (EI): *m/z* 255 (M^+, 0.4%), 224 ($M^+ - CH_3O$, 3%), and 84 ($C_4H_6NO^+$, 100%). MS (CI): *m/z* 256 (MH^+, 100%), 284 ($M^+ + C_2H_5$, 25%), 296 ($M^+ + C_3H_5$, 9%), 224 ($M^+ - CH_3O$, 61%), and 84 ($C_4H_6NO^+$, 1%).

The 5-(9-methyl nonanoate)-3-pentyl-Δ^2-isoxazoline (**4b**) purified by column chromatography: ^{1}H NMR δ 4.55–4.45 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.67 (*s*, 3H, OC*H*$_3$), 2.95 (*dd*, 1H, *J* = 16.7 and 10.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.53 (*dd*, 1H, *J* = 16.8 and 8.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.35–2.25 (*m*, 4H, CH_2–C*H*$_2$–COOMe and –C(=N)–C*H*$_2$–CH_2–), 1.70–1.20 (*m*, 20H, alkyl chain H), 0.90 (*t*, 3H, *J* = 6.9 Hz, –CH_2–C*H*$_3$). ^{13}C

NMR: δ 174.3 (*C*=O), 158.9 (*C*=N), 80.0 (CH_2–H*C*(O)–CH_2), 51.4 (O–*C*H_3), 42.1, 35.2, 34.7, 31.7, 29.4, 29.3, 29.1, 28.9, 27.8, 26.4, 25.5, 24.9, 22.6, 14.0 (–*C*H_3). IR (NaCl) cm^{-1}: 2930, 2857, 1740 (C=O), 1622 (C=N). 5-(9-Methyl nonanoate)-3-pentyl-Δ^2-isoxazoline GC retention time 15.1 min. MS (EI): *m/z* 311 (M^+, 2%), 280 ($M^+ - CH_3O$, 2%) and 140 ($C_8H_{14}NO^+$, 100%). MS (CI): *m/z* 312 (MH^+, 100%), 340 ($M^+ + C_2H_5$, 17%), 352 ($M^+ + C_3H_5$, 6%), 280 ($M^+ - CH_3O$, 11%), and 140 ($C_8H_{14}NO^+$, 3%).

The 5-(9-methyl nonanoate)-3-hexyl-Δ^2-isoxazoline (**4c**) purified by column chromatography: ^{1}H NMR δ 4.55–4.45 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.68 (*s*, 3H, OC*H*$_3$), 2.96 (*dd*, 1H, *J* = 16.7 and 10.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.54 (*dd*, 1H, *J* = 16.7 and 8.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.36–2.28 (*m*, 4H, CH_2–C*H*$_2$–COOMe and –C(=N)–C*H*$_2$–CH_2–), 1.70–1.20 (*m*, 22H, alkyl chain H), 0.90 (*t*, 3H, *J* = 6.9 Hz, –CH_2–C*H*$_3$). ^{13}C NMR: δ 174.3 (*C*=O), 158.9 (*C*=N), 80.0 (CH_2–H*C*(O)–CH_2), 51.4 (O–*C*H_3), 42.1, 35.2, 34.1, 31.5, 29.4, 29.3, 29.1, 29.1, 28.9, 27.8, 26.4, 25.5, 24.9, 22.5, 14.0 (–*C*H_3). IR (NaCl) cm^{-1}: 2930, 2857, 1740 (C=O), 1622 (C=N). 5-(9-Methyl nonanoate)-3-hexyl-Δ^2-isoxazoline GC retention time 16.6 min. MS (EI): *m/z* 325 (M^+, 2%), 294 ($M^+ - CH_3O$, 0.3%), and 154 ($C_9H_{16}NO^+$, 100%). MS (CI): *m/z* 326 (MH^+, 100%), 354 ($M^+ + C_2H_5$, 17%), 366 ($M^+ + C_3H_5$, 6%), 294 ($M^+ - CH_3O$, 8%), and 154 ($C_9H_{16}NO^+$, 3%).

The 5-(9-methyl nonanoate)-3-heptyl-Δ^2-isoxazoline (**4d**) purified by column chromatography: ^{1}H NMR δ 4.51–4.43 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.64 (*s*, 3H, OC*H*$_3$), 2.92 (*dd*, 1H, *J* = 16.7 and 10.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.50 (*dd*, 1H, *J* = 16.8 and 8.1 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.32–2.25 (*m*, 4H, CH_2–C*H*$_2$–COOMe and –C(=N)–C*H*$_2$–CH_2–), 1.75–1.15 (*m*, 24H, alkyl chain H), 0.85 (*t*, 3H, *J* = 6.9 Hz, –CH_2–C*H*$_3$). ^{13}C NMR: δ 174.3 (*C*=O), 158.9 (*C*=N), 80.0 (CH_2–H*C*(O)–CH_2), 51.4 (O–*C*H_3), 42.0, 35.2, 34.1, 31.7, 29.4, 29.3, 29.2, 29.1, 29.1, 28.9, 27.8, 26.4, 25.5, 24.9, 22.6, 14.0 (–*C*H_3). IR (KBr) cm^{-1}: 2926, 2852, 1738 (C=O), 1632 (C=N). 5-(9-Methyl nonanoate)-3-heptyl-Δ^2-isoxazoline GC retention time 18.5 min. MS (EI): *m/z* 339 (M^+, 2%), 308 ($M^+ - CH_3O$, 1%) and 168 ($C_{10}H_{18}NO^+$, 100%). MS (CI): *m/z* 340 (MH^+, 100%), 368 ($M^+ + C_2H_5$, 16%), 380 ($M^+ + C_3H_5$, 5%), 308 ($M^+ - CH_3O$, 8%), and 168 ($C_{10}H_{18}NO^+$, 4%).

The 5-(9-methyl nonanoate)-3-*t*-butyl-Δ^2-isoxazoline (**4f**) purified by column chromatography: ^{1}H NMR δ 4.51–4.43 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.64 (*s*, 3H, OC*H*$_3$), 2.97 (*dd*, 1H, *J* = 16.5 and 10.0 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.54 (*dd*, 1H, *J* = 16.6 and 8.0 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.28 (*t*, 2H, *J* = 7.5 Hz, CH_2–C*H*$_2$–COOMe), 1.75–1.2 (*m*, 14H, alkyl chain H), 1.17 (*s*, 9H, –C(C*H*$_3$)$_3$). ^{13}C NMR: δ 174.4 (*C*=O), 165.9 (*C*=N), 80.4 (CH_2–H*C*(O)–CH_2), 51.5 (O–*C*H_3), 39.4, 35.2, 34.1, 33.0, 29.4, 29.4, 29.2, 29.1, 28.1, 25.6, 25.0. 5-(9-Methyl nonanoate)-3-*t*-butyl-Δ^2-isoxazoline GC retention time 12.7 min. IR (NaCl) cm^{-1}: 2931, 2857, 1740 (C=O), 1609 (C=N). MS (EI): *m/z* 297 (M^+, 2%), 240 ($M^+ - C_4H_9$, 1%), and 126 ($C_7H_{12}NO^+$, 100%). MS (CI): *m/z* 298 (MH^+, 100%), 326 ($M + C_2H_5$, 12%), 338 ($M + C_3H_5$, 3%), and 126 ($C_7H_{12}NO^+$, 2%).

Representative procedure for the synthesis of Δ^2-isoxazolines from methyl 10-undecenoate and syn*-benzaldehyde oxime using* N*-chlorosuccinimide* (9). To a stirred mixture of *N*-chlorosuccinimide (NCS; 1.10 g, 8.1 mmol), pyridine (38 μL, 0.47 mmol), in dry chloroform (7.5 mL) at 24°C was added *syn*-benzaldehyde oxime (1.0 g, 8.2 mmol) in one portion. The mixture was allowed to stir *ca.* 20 min, after which time the suspended NCS had disappeared. Methyl 10-undecenoate (2.0 g, 10.1 mmol) was added, and the temperature raised to 50°C. Triethylamine (1.17 mL, 8.4 mmol) in $CHCl_3$ (2 mL) was added dropwise over 30–35 min, and the reaction solution was then stirred at 50°C for 4.5 h. The reaction solution was cooled, washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated *in vacuo* to obtain 3.0 g of a crude oil. One recrystallization from methanol gave 1.04 g of **4e** as white crystals (41%), m.p.: 59–60°C.

*Representative procedure for the synthesis of 5-(9-methyl nonanoate)-3-carbalkoxy-Δ^2-isoxazoline **4g** and **4h** from methyl 10-undecenoate and alkylchlorooximidoacetate.* To a vigorously stirred solution of methyl 10-undecenoate (1.08 g, 5.5 mmol) and ethyl chlorooximidoacetate (763 mg, 5.1 mmol) in ethyl ether (14 mL) was added a solution of triethylamine (700 μL, 5.02 mmol) in ethyl ether (10 mL) dropwise at room temperature over 1 h. A white precipitate formed upon triethylamine addition. After stirring an additional 2 h, the reaction mixture was taken up in water (10 mL) and extracted with ethyl ether (3 × 30 mL). The combined ether extracts were washed with water (10 mL), dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel as described for the previous isoxazolines. Product **4g** (1.1 g, 66%) was obtained as a clear oil.

^{1}H NMR of 5-(9-methyl nonanoate)-3-carbethoxy-Δ^2-isoxazoline (**4g**): δ 4.70–4.80 (*m*, 1H, CH_2–*H*C(O)–CH_2), 4.30 (*q*, 2H, *J* = 10.71 and 7.1 Hz, –OC*H*$_2$CH$_3$), 3.62 (*s*, 3H, OC*H*$_3$), 3.21 (*dd*, 1H, *J* = 17.5 and 10.9 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.79 (*dd*, 1H, *J* = 17.5 and 8.5 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.26 (*t*, 2H, *J* = 7.5 Hz, CH_2–C*H*$_2$–COOMe), 1.80–1.10 (*m*, 17H, alkyl chain H and –O–CH_2–C*H*$_3$). ^{13}C NMR: δ 174.1 (*C*=O, methyl ester), 160.8 (C=O, ethyl ester), 151.2 (*C*=N), 84.0 (CH_2–H*C*(O)–CH_2), 61.9 (–O–*C*H$_2$CH$_3$), 51.3 (O–*C*H_3), 38.2, 34.9, 33.9, 29.1, 29.1, 28.9, 28.9, 24.9, 24.7, 14.0 (–*C*H_3). IR (NaCl) cm^{-1}: 2932, 2857, 1739 (C=O), 1721 (C=O), 1587 (C=N). 5-(9-Methyl nonanoate)-3-carbethoxy-Δ^2-isoxazoline GC retention time 14.53 min. MS (EI): *m/z* 314 (MH^+, 2%), 282 ($M^+ - CH_3O$, 4%), 240 ($M^+ - C_2H_5O_2$, 7%), and 142 ($C_6H_8NO_3^+$, 100%). MS (CI): *m/z* 314 (MH^+, 66%), 342 ($M^+ + C_2H_5$, 25%), 354 ($M^+ + C_3H_5$, 7%), 282 ($M^+ - CH_3O$, 100%).

The 5-(9-methyl nonanoate)-3-carbmethoxy-Δ^2-isoxazoline (**4h**) purified by column chromatography: ^{1}H NMR δ 4.72–4.85 (*m*, 1H, CH_2–*H*C(O)–CH_2), 3.87 (*s*, 3H, OC*H*$_3$), 3.65 (*s*, 3H, OC*H*$_3$), 3.23 (*dd*, 1H, *J* = 17.5 and 10.9 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.82 (*dd*, 1H, *J* = 17.5 and 8.5 Hz, –(O)CH–C*H*$_2$–C(=N)–), 2.29 (*t*, 2H, *J* = 7.5 Hz, CH_2–C*H*$_2$–COOMe), 1.90–1.10 (*m*, 14H, alkyl chain H). ^{13}C NMR: δ 174.2 (*C*=O, methyl ester), 161.2 (C=O, methyl ester), 151.1 (*C*=N), 84.2 (CH_2–H*C*(O)–CH_2), 52.7 (O–*C*H_3),

51.4 (O–*C*H_3), 38.3, 35.0, 34.0, 29.2, 29.2, 29.0, 29.0, 24.5, 24.9. IR (KBr) cm^{-1}: 2994, 2914, 2852, 1739 (C=O), 1720 (C=O), 1582 (C=N). 5-(9-Methyl nonanoate)-3-carbmethoxy-Δ^2-isoxazoline GC retention time 13.6 min. MS (EI): *m/z* 300 (MH^+, 1%), 282 ($M^+ - CH_3O$, 5%), 240 ($M^+ - C_2H_3O_2$, 4%), and 128 ($C_5H_6NO_3^+$, 100%). MS (CI): *m/z* 300 (MH^+, 26%), 328 ($M^+ + C_2H_5$, 18%), 340 ($M^+ + C_3H_5$, 5%), and 286 ($M^+ - CH_3O$, 100%).

RESULTS AND DISCUSSION

Scheme 1 depicts the reaction sequence initially utilized to synthesize Δ^2-isoxazolines by 1,3-dipolar cycloaddition between nitrile oxides, **2**, and methyl 10-undecenoate, **3**. Although two regioisomers, namely, the 3,5-substituted and 3,4-substituted isoxazolines, **4** and **5**, respectively, are possible from the reaction, nitrile oxide cycloadditions to terminal olefins are highly regioselective and give predominantly 3,5-substituted isoxazolines (1). In this respect, methyl 10-undecenoate behaved as a typical monosubstituted olefin and gave **4** as the only observable isoxazoline. These reactions proceed smoothly and represent a convenient way to synthesize fatty compounds containing the Δ^2-isoxazoline ring system. As can be seen in Table 1 (entries **4a**–**4f**), the Δ^2-isoxazolines are obtained in good yields after purification by silica gel chromatography.

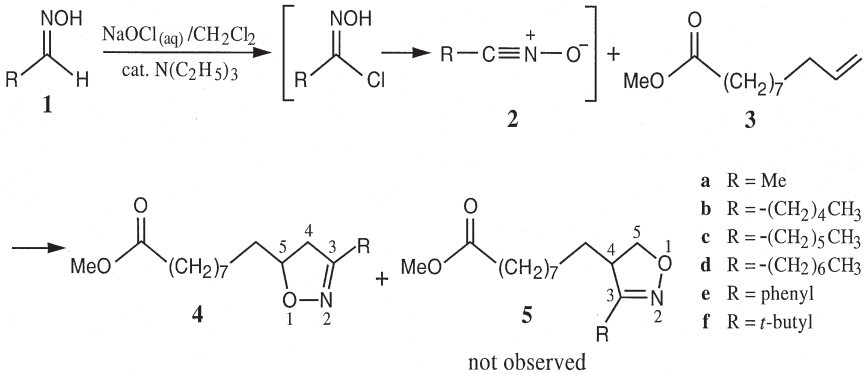
GC and ^{1}H NMR analyses of the crude isoxazoline product mixtures obtained from these reactions confirmed that the cycloaddition reactions gave only one regioisomer. Also tabulated in Table 1 are the ^{1}H NMR chemical shifts for the 4- and 5-ring hydrogens of compounds **4** (Scheme 1). Comparison of these data obtained for the purified isoxazolines with ^{1}H NMR data for analogous Δ^2-isoxazolines found in the literature (9) helped establish that the 3,5-substituted regioisomer, **4**, was formed exclusively.

In addition to the isoxazolines, unreacted starting olefin, easily recovered during silica gel chromatography, is the other main material observed from these reactions. Small amounts of furoxans, from nitrile oxide dimerization, were also retrieved by chromatography. Chlorinated olefin and subsequent chlorhydrin products formed by reaction with NaOCl were not observed since the organic phase of the biphasic reaction mixture appears to effectively protect the hydrophobic fatty ester from the aqueous NaOCl phase. Chlorination of the aldoxime in the aqueous NaOCl followed by HCl elimination gives the reactive nitrile oxide intermediate *in situ*. Migration of the nitrile oxide into the methylene chloride phase allows it to be trapped by the olefinic substrate. Interestingly, when we used acetaldoxime as the nitrile oxide precursor, only low yields (23%) of **4a** were obtained (Table 1, entry **4a**) relative to the other nitrile oxide precursors. Presumably, the high solubility of acetaldoxime and its corresponding nitrile oxide in the reaction mixture's aqueous phase prevents efficient partitioning into the organic phase where it can be efficiently trapped by the olefinic substrate.

To examine if the isoxazoline yields could be improved, isoxazoline formation was briefly examined by generating nitrile oxides from aldoximes under nonaqueous reaction conditions using *N*-chlorosuccinimide at 50°C in anhydrous $CHCl_3$ following the procedure of Larsen and Torssell (9). The yields for the two reactions examined by this method are also shown in Table 1 (yields in parentheses). As can be seen, the yield of **4a** improves significantly while the yield for **4c** remains approximately equal to the yield obtained by the other method. The improved yield of **4a** obtained from acetaldoxime under these conditions confirms, in part, our earlier suspicions that acetaldoxime's hydrophilic nature may have prevented the reaction from taking place in the biphasic reaction conditions.

Because nitrile oxides readily dimerize to furoxans, one commonly used technique to slow down the rate of furoxan formation relative to the desired 1,3-dipolar cycloaddition is to use hindered nitrile oxides. The isoxazoline yields reported in Table 1 support this notion. As can be seen, the yields improve as the steric hindrance of the nitrile oxide increases in the order, Me < alkyl < phenyl < *t*-butyl (the R group shown in Table 1 is derived from the nitrile oxide). Accordingly, the half-life for acetonitrile oxide (R = Me) has been reported to be <1 min (10), benzonitrile oxide's (R = phenyl) half-life is 30–60 min (10), and 2,2-dimethylpropanenitrile oxide (R = *t*-butyl) has been reported to be 9 d (6). Thus, the longer the nitrile oxide can persist in solution without undergoing dimerization, the greater the likelihood that it can be trapped by the terminal olefin to produce isoxazolines.

The only other example we found where nitrile oxides are used to make isoxazoline fatty compounds was reported by



SCHEME 1

TABLE 1
Yields, Melting Points, and ^{1}H NMR Data for Δ^2-Isoxazoline (4) Obtained from the Cycloaddition Between Nitrile Oxides 2 and Methyl 10-Undecenoate

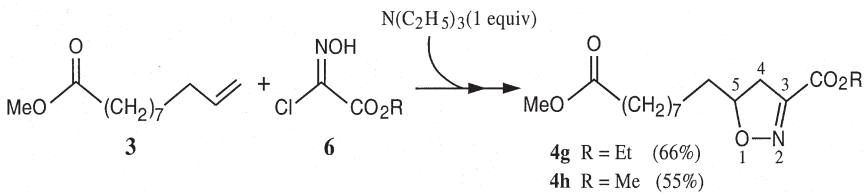
Δ^2-Isoxazolines (4)	Yield[a,b] (%)	m.p. (°C)	^{1}H NMR[c] δ, *J* (Hz) ring H (5-position)	^{1}H NMR[c] δ, *J* (Hz) ring H (4-position)
4a, R = Me	23 (40)	Oil	4.55–4.45 (*m*, 1H)	2.94 (*dd*, 1H, *J* = 16.8 and 10.1) 2.51 (*dd*, 1H, *J* = 16.9 and 8.2)
4b, R = $-(CH_2)_4CH_3$	65	Oil	4.55–4.45 (*m*, 1H)	2.95 (*dd*, 1H, *J* = 16.7 and 10.1) 2.53 (*dd*, 1H, *J* = 16.8 and 8.1)
4c, R = $-(CH_2)_5CH_3$	63 (66)	Melts at rt	4.55–4.45 (*m*, 1H)	2.96 (*dd*, 1H, *J* = 16.7 and 10.1) 2.54 (*dd*, 1H, *J* = 16.7 and 8.1)
4d, R = $-(CH_2)_6CH_3$	64	29–30	4.51-4.43 (*m*, 1H)	2.92 (*dd*, 1H, *J* = 16.7 and 10.1) 2.50 (*dd*, 1H, *J* = 16.8 and 8.1)
4e, R = Phenyl	74	59–60	4.75–4.72 (*m*, 1H)	3.40 (*dd*, 1H, *J* = 16.4 and 10.3) 2.98 (*dd*, 1H, *J* = 16.4 and 8.2)
4f, R = *t*-Butyl	85	Melts at rt	4.51–4.43 (*m*, 1H)	2.97 (*dd*, 1H, *J* = 16.5 and 10.0) 2.54 (*dd*, 1H, *J* = 16.6 and 8.0)
4g,[d] R = $-CO_2Et$	66	Oil[e]	4.70–4.80 (*m*, 1H)	3.21 (*dd*, 1H, *J* = 17.5 and 10.9) 2.79 (*dd*, 1H, *J* = 17.5 and 8.5)
4h,[d] R = $-CO_2Me$	55	56–58	4.72–4.85 (*m*, 1H)	3.23 (*dd*, 1H, *J* = 17.5 and 10.9) 2.82 (*dd*, 1H, *J* = 17.5 and 8.5)

[a]Isolated yields.
[b]Yields in parentheses obtained by reacting aldoximes with *N*-chlorosuccinimide in $CHCl_3$ at 50°C following the procedure of Larsen and Torssell (9).
[c]Spectra taken in $CDCl_3$ at 400 MHz. NMR, nuclear magnetic resonance.
[d]Prepared from the corresponding hydroximic acid chlorides; see Experimental Procedures section.
[e]All attempts to recrystallize **4g** failed.

Ahmed *et al.* (16). Interestingly, they reported the 1,3-cycloaddition between methyl 10-undecenoate and nitrile oxide $MeOOCC{\equiv}N^+{-}O^-$, obtained from the reaction of methyl chlorooximidoacetate with base, gave the 3,4-substituted regioisomer exclusively in 90% yield. These authors may have inadvertently reported the wrong structure for the isoxazoline they prepared. Because their result seemingly contradicts the large body of knowledge regarding nitrile oxide cycloadditions to monosubstituted olefins, we repeated their research by synthesizing isoxazolines **4g** and **4h** with both the carbmethoxy and carbethoxy functionality substituted at the 3-position of the isoxazoline ring. Because the aldehydes needed to prepare the starting oximes required for the biphasic reaction were not readily available, we opted to generate and trap the nitrile oxides by treating their corresponding hydroximic acid chlorides, which were easily prepared, with base in the presence of methyl 10-undecenoate (Scheme 2).

Accordingly, the ethyl and methyl hydroximic acid chlorides, **6g** and **6h**, were prepared by treating their corresponding glycine ester hydrochlorides with sodium nitrite in an aqueous HCl solution (14). Both the methyl and ethyl hydroximic acid chlorides are crystalline compounds, although the ethyl hydroximic acid chloride was much easier to handle since the methyl hydroximic acid chloride is very hygroscopic.

As can be seen from Table 1 (entries **4g** and **4h**), in our hands, the isoxazoline yields obtained from these reactions were somewhat lower than those reported by Ahmed *et al.* (16), 66% and 55% for **4g** and **4h**, respectively. We suspect the lower yields obtained using **6h** relative to **6g** result from the difficulty in handling the hygroscopic reagent. The chemical shifts and coupling constants determined from ^{1}H NMR analyses of purified isoxazoline **4h** are similar to those reported by Ahmed *et al.* (16) and to the other isoxazoline ring hydrogens reported in this work (Table 1). Additionally, the chemical shift, splitting patterns, and coupling constant values for the isoxazoline ring hydrogens of **5h** would be substantially different from what was observed. Based on these observations and the known regioselectivity of nitrile oxides toward terminal olefins,



SCHEME 2

it is most likely that **4h**, not **5h** (Scheme 1, R = CO_2R), is the correct isoxazoline structure obtained from these reactions.

In conclusion, nitrile oxides react readily with the terminal olefin, methyl 10-undecenoate, to give good yields of 3,5-substituted Δ^2-isoxazolines under mild reaction conditions. These long-chain fatty ester isoxazolines may have interesting biological and industrial applications, and may also be used as intermediates to derive new oleochemicals with interesting properties not easily obtainable by other methods.

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