Reduction of Fatty Ester $\Delta^2$-Isoxazoline Heterocycles.
Preparation of Fatty Esters Containing the
$\beta$-Hydroxy Ketone Moiety

James A. Kenar*

NCAUR, ARS, USDA, Food and Industrial Oil Research, Peoria, Illinois 61604

ABSTRACT: Fatty ester compounds containing the $\beta$-hydroxy ketone moiety were prepared in good yields from their corresponding fatty $\Delta^2$-isoxazoline heterocyclic precursors by a reductive hydrogenolysis–hydrolysis procedure using Raney nickel as catalyst. By this methodology, C-17, C-18, and C-19 straight-chain fatty methyl esters containing the 10-hydroxy 12-keto moieties were prepared in 73, 83, and 92%, respectively, from their corresponding isoxazoline fatty ester compounds. Two other 10-hydroxy 12-keto C-12 and C-14 fatty ester compounds were prepared in 84 and 92% yield, respectively. The C-12 $\beta$-hydroxy ketone contains a phenyl ring at C-12, whereas the C-14 $\beta$-hydroxy ketone compound has two methyl substituents at C-13. GC–MS using electron impact ionization was used to determine the hydroxyl and ketone positions after conversion of the hydroxyl group into its corresponding trimethylsilyl ether. The precursor fatty ester $\Delta^2$-isoxazolines used in this study are readily available in one step from a 1,3-dipolar cycloaddition reaction between nitrile oxides and methyl 10-undecenoate. This overall two-step sequence, 1,3-dipolar cycloaddition followed by reductive ring opening, represents a convenient method to construct fatty ester compounds in good yields containing the $\beta$-hydroxy ketone functionality, an outcome not easily accessible by other methods.


KEY WORDS: Fatty ester $\beta$-hydroxy ketones, 1,3-cycloaddition, $\Delta^2$-isoxazolines, mass spectrometry, methyl 10-hydroxy-12-ketomargarate, methyl 10-hydroxy-12-ketononadecanoate, methyl 10-hydroxy-12-ketostearate, nitrile oxides, Raney nickel, reductive hydrogenolysis–hydrolysis.

In pursuit of new strategies to functionalize fatty ester compounds and derive new oleochemicals with potentially useful chemical and physical properties, we have been interested in examining transformations available to fatty ester $\Delta^2$-isoxazoline heterocycles (4,5-dihydroisoxazoles). Recently, a series of fatty ester $\Delta^2$-isoxazoline compounds, 3, containing the isoxazoline heterocycle in the alkyl chain, were prepared in good yields through a regioselective 1,3-dipolar cycloaddition reaction between methyl 10-undecenoate (1) and various nitrile oxides (2), generated in situ (Scheme 1).

The $\Delta^2$-isoxazoline heterocycle has found widespread application in organic chemistry due to its versatility as a synthetic intermediate, the ease with which it can be prepared, and the availability of starting materials needed for its preparation (2,3). The chemical transformations available to the $\Delta^2$-isoxazoline heterocycle include alkylation (4), dehydrogenation to isoxazoles (5,6), and reductive cleavage to yield such functional groups as $\beta$-hydroxy carbonyls (7–12) or $\gamma$-amino alcohols (13). Because of the diverse chemical transformations available to the isoxazoline ring, fatty compounds possessing this heterocycle represent attractive intermediates from which to obtain new types of functionalized fatty compounds.

We now report on the Raney nickel-mediated reductive hydrogenolysis–hydrolysis of fatty ester isoxazoline precursors to prepare fatty ester compounds containing the $\beta$-hydroxy ketone functionality. This ring-opening reaction, in conjunction with the facile preparation of the fatty ester $\Delta^2$-isoxazoline precursors, represents a straightforward method to prepare $\beta$-hydroxy ketone-containing fatty compounds in overall yields ranging from 48 to 78% for the two steps starting from methyl 10-undecenoate.

EXPERIMENTAL PROCEDURES

Materials. All $\Delta^2$-isoxazolines were prepared as previously reported (1) and purified before use. Chemicals purchased from Aldrich Chemical Co. (Milwaukee, WI) were used without further purification unless otherwise noted. Methanol, THF, methylene chloride, hexane, and boric acid were obtained from Fisher Scientific Co. (Fairlawn, NJ) and Sylon BTZ trimethylsilyl silylating reagent was from Supelco (Bellefonte, PA).

NMR. $^1$H NMR and $^{13}$C NMR spectra were recorded using a Bruker ARX 400 spectrometer (Billerica, MA) with a 5-mm dual proton/carbon probe (400 MHz $^1$H/100.61 MHz $^{13}$C) using CDCl$_3$ as solvent.

FTIR. IR spectra were obtained using a PerkinElmer (Norwalk, CT) Spectrum RX FTIR spectrophotometer. Samples were analyzed as either a film on NaCl plates (liquids) or in a KBr matrix (solids).

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

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

GC–MS analyses were conducted using a Hewlett-Packard 5890 Plus GC (Hewlett-Packard 5890B mass spectrometer). Electron ionization (EI) was performed at 70 eV using a mass range of 50–550 amu. GC conditions: helium head pressure 3 psi (155 kPa); injector temperature set at 250°C; transfer line temperature (EI) was performed at 70 eV using a mass range of 50–550 amu. GC–MS (EI) was performed at 70 eV using a mass range of 50–550 amu. GC was performed with a Hewlett-Packard 5890 Series II Plus GC (Hewlett-Packard 5890B column: 30 m × 0.25 mm i.d.; Hewlett-Packard Co.) coupled with a Hewlett-Packard 5989B mass spectrometer. Electron ionization (EI) was performed at 70 eV using a mass range of 50–550 amu. GC conditions: helium head pressure 3 psi (155 torr); injector temperature set at 250°C; transfer line temperature set at 280°C; the oven temperature program was identical to that described in the GC section.

TLC. Analytical TLC was carried out on silica gel 60F254 (250 µm) plates purchased from Alltech Associates Inc. (Waukegan, IL). The eluent used to develop the plates was a 30:70 mixture of ethyl ether/hexane.

Representative procedure for the Raney nickel/boric acid reduction of α,β-unsaturated ketones to β-hydroxy ketones (8,9). To a solution of 5-(9-methyl nonanoate)-3-heptyl-Δ2-isoxazoline (3c) (151 mg, 0.446 mmol), in methanol (4.2 mL) and water (700 µL) (MeOH/H2O = 6:1), was added boric acid (59.6 mg, 0.964 mmol) and a spatula tip (ca. 10–20 mg) of Raney nickel. The reaction vessel’s atmosphere was replaced with hydrogen gas by repeated evacuation and flushing with hydrogen (six to ten times); a balloon filled with H2 was used to maintain the reaction flask’s H2 atmosphere. The mixture was stirred vigorously for 22 h at room temperature (rt), and then filtered through a coarse glass frit into a separatory funnel containing water (10 mL) and CH2Cl2 (20 mL). The layers were separated, the aqueous layer was extracted with CH2Cl2 (2 × 10 mL) and the combined organic extracts were washed with saturated NaCl solution, dried over Na2SO4, and concentrated in vacuo to give 140 mg (92% yield) of an off-white solid that appeared pure by 1H NMR. An analytical sample was obtained by recrystallization from methanol/H2O to give 3c as white crystals.

Representative procedure for the trimethylsilyl (TMS) derivatization of β-hydroxy keto fatty esters. In a small vial, the β-hydroxy keto fatty ester (~10 mg) was dissolved in 500 µL of hexane. Sylon BTZ silylating reagent (50 µL) was added, the vial sealed then shaken, and the solution was allowed to stand for 10 min at 22°C. The resulting solution, without further preparation, was analyzed by GC and/or GC–MS.

1H NMR of methyl 10-hydroxy-12-keto nonadecanoate (5c): δ 4.00 [broad m, 1H, –CH2(CHOH)CH2–], 3.65 (s, 3H, –OCH3), 3.10–3.00 [broad m, 3H, –OH], 3.06 (s, 1H, –OH), 2.58 [dd, 1H, J = 17.5 and 2.8 Hz, –HOCH2CH2C(=O)=–], 2.47 [dd, 1H, J = 17.6 and 9.1 Hz, –HOCH2CH2C(=O)=–], 2.40 [t, 2H, J = 7.5 Hz, –CH2–CH2–COOMe], 1.8–1.1 (m, 24H, alkyl chain H), 0.86 (s, 3H, J = 6.9 Hz, –CH3). 13C NMR: δ 212.7 (C=O, ketone), 174.3 (C=O ester), 67.6 (–C5H11O, 100%), 243 (C13H27O2Si, 39%), 127 (C9H17O, 100%), 215 (M+ – C10H18, 21%), 315 (M+ – C5H11, 11%), 273 (M+ – C7H13O, 21%), 215 (M+ – C9H17O, 21%), 243 (C13H27O2Si, 39%), 127 (C9H17O, 100%).

1H NMR of methyl 10-hydroxy-12-keto heptadecanoate (5a): δ 4.00 [broad m, 1H, –CH2(CHOH)CH2–], 3.65 (s, 3H, –OCH3), 3.06 (s, 1H, –OH), 2.58 [dd, 1H, J = 17.6 and 2.8 Hz, –HOCH2CH2C(=O)=–], 2.47 [dd, 1H, J = 17.6 and 9.1 Hz, –HOCH2CH2C(=O)=–], 2.40 [t, 2H, J = 7.5 Hz, –HOCH2CH2C(=O)=–], 2.28 [t, 2H, J = 7.5 Hz, –CH2–CH2–COOMe], 1.8–1.1 (m, 20H, alkyl chain H), 0.87 (s, 3H, J = 7.0 Hz, –CH3). 13C NMR: δ 212.6 (C=O, ketone), 174.3 (C=O ester), 67.6 (C17H35O, 15%), 273 (C17H35O2Si, 39%), 127 (C9H17O, 100%).
PREPARATION OF FATTY ESTER β-HYDROXY KETONES

RESULTS AND DISCUSSION

Fatty compounds containing hydroxy (14) or keto (15–18) groups are well documented and have been thoroughly characterized (19,20). Several research groups have reported the synthesis of fatty compounds containing both a hydroxy and a keto group in the alkyl chain (21–23), although we could find no references describing fatty compounds containing the hydroxy and keto moieties in a 1,3-position (β-hydroxy ketones) relative to one another. This work describes the second step of a facile two-step synthesis to prepare such compounds as well as their characterization.

Several methods based on AlCl3 (11), titanous chloride (24), Raney nickel (7–12), ozone (11), or peracids (25) can be used to convert the isoxazoline ring into β-hydroxy carbonyl compounds by cleaving the isoxazoline’s weak N-O bond. We utilized the Raney nickel procedure outlined by Curran and coworkers (7–9) because it appeared to be most convenient for the isoxazoline ring to the carbonyl compound. We used the Raney nickel procedure outlined by Curran and coworkers (7–9) because it appeared to be most suitable based on the mild reaction conditions and short reaction times. Scheme 2 depicts the general reaction sequence utilized to convert the fatty ester $\Delta^2$-isoxazoline compounds, as well as their characterization.

![Scheme 2](image-url)
positive EI GC–MS. The electron impact mass spectra for derivatives in and ketone moieties in their alkyl chains, the hydroxyl groups ester compounds and determine the position of the hydroxy isoxazoline using MeOH/H2O at 6:1 failed because the addition of a phenyl ring. Initial attempts to reductively cleave this with which to dissolve nature of the reaction mixture. By using THF (a better solvent for the conversion of isoxazolines into β-hydroxy ketones are listed in Table 1. During the course of this research, no evidence of intermediate 3e was observed under the conditions utilized to perform the desired transformations.

The MeOH/H2O reaction medium was well suited for all the isoxazolines utilized except isoxazoline 3e, which contained a phenyl ring. Initial attempts to reductively cleave this isoxazoline using MeOH/H2O at 6:1 failed because the addition of water prompted precipitation of the dissolved isoxazoline. Efficient reaction of 3e with hydrogen (Raney nickel catalyst) was thus not possible due to the heterogeneous nature of the reaction mixture. By using THF (a better solvent with which to dissolve 3e) rather than MeOH, the precipitation of 3e was avoided and the reaction completed.

To confirm the structures of the β-hydroxy ketone fatty ester compounds and determine the position of the hydroxy and ketone moieties in their alkyl chains, the hydroxyl groups in 5a–e were converted to their corresponding trimethylsilyl derivatives 6a–e (Scheme 2) and subsequently analyzed by positive EI GC–MS. The electron impact mass spectra for 6b, shown in Figure 1, illustrates the observed fragment ions derived from this molecule and is demonstrative of all the β-hydroxy ketone fatty ester compounds (6a–e) examined.

As can be seen for 6b, the [M]+ and [M + H]+ molecular ions are in very low abundance, a commonly observed trend for trimethylsilyl-containing compounds (26). This was also found to be the case for 6a and 6c–e. Another prominent fragment ion, typically observed for compounds containing the trimethylsilyl group, is the [M – CH3]+ ion generated by loss of a methyl group from the silicon atom (26). In the case of 6b, this cleavage gives an m/z 385 ion in 31% relative abundance (cleavage A, Fig. 1). Fragmentation along the fatty compound alkyl chain occurs selectively as evidenced by cleavages B and C α to the ketone moiety. Cleavage B (due to loss of a C6H13 fragment) affords a C14H29O4Si m/z 315 fragment ion with a relative abundance of 17%. Likewise, cleavage at location C results in a C7H13O3Si fragment ion with m/z 113 and represents the base peak at 100% relative abundance. Cleavage also occurs predominantly α to the trimethylsilyl ether group at cleavage sites D and E. Cleavage at D gives loss of a C6H13O fragment and results in a C14H29O4Si m/z 273 fragment ion in 17% relative abundance; cleavage at E (loss of C10H20O fragment) gives a C12H25O2Si molecular ion with m/z 229 in 48% relative abundance. From these fragmentation patterns, the trimethylsilyl ether group and the ketone positions are readily established to be at the C-10 and C-12 carbons of the alkyl chain in 6b, respectively. Similar interpretations of the mass spectra for compounds 6a and 6c–e indicate their trimethylsilyl ether and ketone groups, respectively, are located at the C-10 and C-12 carbons of the alkyl chain. Moreover, from these analyses it is apparent the hydroxy and ketone positions in fatty β-hydroxy ketones 5a–e are located at the same positions along the alkyl chains as determined in 6a–e.

### TABLE 1

<table>
<thead>
<tr>
<th>β-Hydroxy ketone</th>
<th>Reaction time (h)</th>
<th>Solvent system</th>
<th>Yielda (%)</th>
<th>m.p. b (°C)</th>
<th>13C NMR signalsc (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbonyl</td>
<td>-OH(Ph)</td>
</tr>
<tr>
<td>5a, R –(CH2)4CH3</td>
<td>18</td>
<td>MeOH/H2O (5:8:1)</td>
<td>73</td>
<td>42–43</td>
<td>67.6</td>
</tr>
<tr>
<td>5b, R –(CH2)5CH3</td>
<td>20</td>
<td>MeOH/H2O (5:8:1)</td>
<td>83</td>
<td>49–49.5</td>
<td>67.6</td>
</tr>
<tr>
<td>5c, R –(CH2)6CH3</td>
<td>22</td>
<td>MeOH/H2O (6:1)</td>
<td>92</td>
<td>50–51</td>
<td>67.6</td>
</tr>
<tr>
<td>5d, R = t-Butyl</td>
<td>17</td>
<td>MeOH/H2O (5:1)</td>
<td>92</td>
<td>ca. 10</td>
<td>67.8</td>
</tr>
<tr>
<td>5e, R = Phenyl</td>
<td>21</td>
<td>THF/H2O (5:8:1)</td>
<td>84</td>
<td>53–55</td>
<td>67.8</td>
</tr>
</tbody>
</table>

aIsolated yields.
bMelting points obtained from recrystallized samples.
cNMR spectrum obtained with CDCl3 as solvent.
Also shown in Table 1 are the $^{13}$C NMR signal assignments for the carbinyl [–CH(OH)–] and the carbonyl carbons [–C=O–] in the alkyl chain of the β-hydroxy ketone fatty compounds, 5a–e. As can be seen, the carbinyl carbon’s chemical shift is nearly identical regardless of the terminal R group. On the other hand, the carbonyl carbon’s chemical shift is quite dependent upon the nature of the terminal R group, most likely because of its proximity to the R group. It is interesting to note the upfield ($\delta$ 201 ppm) and downfield ($\delta$ 218 ppm) chemical shifts between the carbonyl carbon in 5d (R = tert-butyl) and 5e (R = phenyl), respectively, relative to the carbonyl carbon signal in 5a–c (R = alkyl) at $\delta$ 212 ppm.

Insight into how the relative 1,3-proximity of the hydroxyl and ketone groups affects the $^{13}$C chemical shifts for the carbinyl and carbonyl carbons can be gained by comparing the chemical shift data obtained for methyl 10-hydroxy-12-keto octadecanoate (5b) with the data presented by Tulloch for methyl 10-hydroxy-octadecanoate (19) and methyl 12-oxooctadecanoate (20) as shown in Table 2.

As can be seen, the $^{13}$C chemical shift for the C-10 carbinyl carbon in 5b is moved upfield 4.2 ppm relative to the C-10 carbinyl carbon in methyl 10-hydroxy-octadecanoate, whereas the carbonyl carbon in 5b is shifted downfield 1.8 ppm relative to methyl 12-oxooctadecanoate. By assuming all other interactions are equal, it appears the carbonyl group in 5b is exerting a definite shielding effect on the C-10 hydroxy carbon, whereas the hydroxyl group is exerting only a slight (negligible) deshielding effect on the C-12 carbonyl carbon.

These Raney nickel-mediated reductions of fatty ester $\Delta^2$-isoxazolines represent a convenient method to unmask the isoxazoline heterocycle and obtain fatty β-hydroxy ketone compounds in good overall yields. The isoxazoline ring opening

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**TABLE 2**

<table>
<thead>
<tr>
<th>Fatty ester</th>
<th>$^{13}$C NMR signals (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-10</td>
</tr>
<tr>
<td></td>
<td>Carbinyl</td>
</tr>
<tr>
<td>Methyl 10-hydroxy-12-octadecanoate</td>
<td>67.6</td>
</tr>
<tr>
<td>Methyl 10-hydroxy-12-octadecanoate</td>
<td>5b</td>
</tr>
<tr>
<td>Methyl 10-hydroxy-12-oxooctadecanoate</td>
<td>71.83</td>
</tr>
<tr>
<td>Methyl 12-oxooctadecanoate</td>
<td></td>
</tr>
<tr>
<td>Methyl 12-oxooctadecanoate</td>
<td></td>
</tr>
</tbody>
</table>

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$^a$All $^{13}$C NMR chemical shifts reported are from spectra obtained in CDCl$_3$.

$^b$See Reference 19.

$^c$See Reference 20.
combined with easy preparation of the precursor fatty ester Δ²-isoxazoline compounds (derived from the reaction between methyl 10-undecenoate and nitrile oxides) makes this overall two-step procedure an attractive way to prepare fatty ester compounds containing the β-hydroxy ketone functionality, an outcome not readily accessible by other approaches.

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REFERENCES


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