COMMUNICATION

Synthesis of pyridazine fatty ester derivatives in water: a sonochemical approach

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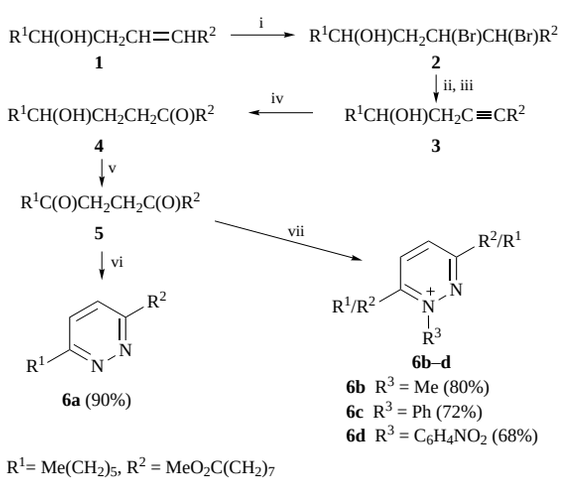
Reactions induced by ultrasonic irradiation of methyl 9,12-dioxostearate with hydrazines in water in the presence of acidic alumina at 0–5 °C provide high yields of pyridazine fatty esters directly.

We have reported the high yielding reaction of 1,3-dioxo fatty esters with hydrazines in water under concomitant ultrasonic irradiation (20 kHz, 53 W cm^{-2}) to give the corresponding pyrazole fatty ester derivatives.[1] One interesting parameter of the reaction conditions in these reactions was the ability to achieve chemical reaction in water under ultrasound with a substrate (methyl 10,12-dioxostearate) that is insoluble in the reaction medium. Here we describe another high-yielding reaction involving 9,12-dioxostearate **5** with hydrazines. Compound **5** was obtained by bromination of methyl ricinoleate [methyl (*Z*)-12-hydroxyoctadec-9-enoate **1**][2] followed by ultrasound-assisted dehydrobromination of the 9,10-dibromo intermediate **2** with ethanolic KOH to give 12-hydroxyoctadec-9-ynoic acid **3**,[3] the methyl ester of which was hydrated using mercury(II) acetate as catalyst to yield methyl 12-hydroxy-9-oxostearate **4**,[4] which was subsequently oxidized with chromic acid to give methyl 9,12-dioxostearate **5** (methyl 9,12-dioxooctadecanoate) (see Scheme 1).[5]



Scheme 1 *Reagents and conditions:* i, Br_2, Et_2O; ii, KOH, EtOH, ultrasound 30 min; iii, BF_3–MeOH; iv, $Hg(OAc)_2$, THF, H_2O, ultrasound 20 min; v, chromic acid, Et_2O; vi, H_2O, alumina, ultrasound 15 min, 0–5 °C, NH_2NH_2; vii, H_2O, alumina, ultrasound 15 min, 0–5 °C, R^3NHNH_2

The general approach to synthesize pyridazines by reaction between hydrazine or substituted hydrazines and 1,4-dioxo substrates proceeds through the formation of dihydropyridazine intermediates, which are dehydrogenated in the presence of air or PtO_2 into pyridazines.[6] Other methods include Diels–Alder reactions.[7,8]

Ultrasonic irradiation of methyl 9,12-dioxostearate in water in the presence of slightly acidic alumina and hydrazine for 15 min at 0–5 °C gave directly the corresponding pyridazine derivatives (**6a**–**d**, 68–90%) after purification (Scheme 1). Product identification was established on the basis of spectral results [high resolution molecular ion mass (M^+) and ^1H and ^{13}C NMR spectroscopy]. When the same reactions were conducted without ultrasound, but stirred vigorously for 3 h at room temperature, no pyridazine derivatives were formed. Also, no dihydropyridazine intermediates were isolated from these reactions.

During sonication of the reaction mixture, the insoluble fatty ester substrate is homogenized, the hydrazines used being water insoluble apart from hydrazine and methylhydrazine. Ultrasonic irradiation gives rise to a high degree of microstreaming and interaction of particles, the reactions appearing to be assisted by the energy generated from cavitational processes.[9]

Experimental

Preparation of methyl 9,12-dioxostearate 5 from methyl ricinoleate

Bromine (5.6 g, 3.5 mmol) was added to a solution of methyl ricinoleate **1** (2.0 g, 6.4 mmol) in Et_2O (30 cm^3) and the mixture stirred for 15 min. It was then successively washed with aqueous $Na_2S_2O_7$ (5%, 10 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated to give crude methyl 9,10-dibromo-12-hydroxystearate **2** as a viscous liquid (3.0 g, 99%); ν_{max}/cm^{-1} 3450, 2950, 2865, 1740, 840, 760, 720; $\delta_H(CDCl_3)$† 0.88 (t, *J* 7.0, 3H, CH_3), 1.2–1.8 (m, 20H), 1.9–2.1 (4H), 2.25 (s, 1H, CHO*H*, D_2O exchangeable), 2.32 (t, *J* 7.0, 2H, 2-*H*), 3.66 (s, 3H, CO_2CH_3), 3.81 (m, 1H, C*H*OH) and 4.65 (m, 2H, C*H*Br); $\delta_C(CDCl_3)$ 14.13 (C-18), 22.52 (C-17), 25.28 (C-3), 25.61 (C-14), 28.95–29.29, 31.85 (C-16), 34.02 (C-2), 37.92 (C-13), 43.72 (C-11), 51.43 (CO_2CH_3), 56.84 (C-10), 60.29 (C-9), 69.76 (C-12) and 174.24 (C-1).

The latter was dissolved in ethanol (95%, 30 cm^3) containing KOH (5.3 g) and the resulting solution sonicated for 30 min using a 20 kHz ultrasound horn (Sonoreactor, Undatum Ultrasonics S.A., Louvain-la-Neuve, Belgium) at ambient temperature. The reaction mixture was acidified with dilute aqueous HCl (6 mol dm^{-3}; 20 cm^3) and extracted with Et_2O (2 × 30 cm^3). The combined extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated. The residue was refluxed with BF_3–MeOH complex (14%, w/w, 5 cm^3) in absolute MeOH (30 cm^3) for 10 min, after which the mixture was diluted with water (50 cm^3) and extracted with Et_2O (2 × 60 cm^3). The combined extracts were evaporated and silica column chromatographic purification of the residue with light petroleum (bp 40–60 °C)–Et_2O (85:15 v/v, 200 cm^3) as eluent gave pure methyl 12-hydroxyoctadec-9-ynoate **3** (1.3 g, 66%); ν_{max}/cm^{-1} 3450, 2950, 2865, 1738, 1460, 1360 and 1170; $\delta_H(CDCl_3)$ 0.88 (t, *J* 7.0, 3H, CH_3), 1.2–1.6 (m, 20H), 2.04 (s, 1H, CHO*H*, D_2O exchangeable), 2.2 (m, 4H), 2.30 (t, *J* 7.0, 2H, 2-*H*), 3.66 (s, CO_2CH_3) and 3.69 (m, 1H, C*H*OH); $\delta_C(CDCl_3)$ 14.11 (C-18), 18.72 (C-8), 22.75 (C-17), 24.91 (C-3), 25.66 (C-14), 27.95 (C-11), 28.75–29.15, 31.91 (C-16), 34.02 (C-2), 36.21 (C-13), 51.42 (CO_2CH_3), 70.37 (C-12), 78.24 (C-10), 82.41 (C-9) and 174.23 (C-1).

A mixture of the ester **3** (1.0 g, 3.2 mmol), tetrahydrofuran

† *J* Values are given in Hz.

(10 cm^3), water (10 cm^3) and $Hg(OAc)_2$ (2.0 g, 6.27 mmol) was sonicated at ambient temperature for 20 min. The reaction mixture was acidified with dilute HCl (6 mol dm^{-3}; 10 cm^3) and the solution extracted with Et_2O (3 × 30 cm^3). The ethereal extract was washed with water (20 cm^3) and dried ($NaSO_4$). The filtrate was evaporated to give methyl 12-hydroxy-9-oxostearate **4** as a white solid (1.0 g, 95%), mp 52–53 °C; ν_{max}/cm^{-1} 3500, 2940, 2860, 1740, 1700, 1440, 1150 and 760; $\delta_H(CDCl_3)$ 0.88 (t, *J* 7.0, 3H, C*H*$_3$), 1.2–1.6 (m, 22H), 2.1 (s, 1H, CHO*H*, D_2O exchangeable), 2.30 (t, *J* 7.0, 2H, 2-*H*), 2.5 (t, *J* 6.8, 4H, 8-*H*, 10-*H*), 3.5 (m, 1H, C*H*OH) and 3.66 (s, 3H, CO_2CH_3); $\delta_C(CDCl_3)$ 14.03 (C-18), 22.59 (C-17), 23.83 (C-7), 24.86 (C-3), 25.67 (C-14), 28.98–29.90, 30.98 (C-11), 31.85 (C-16), 34.07 (C-2), 37.80 (C-13), 39.10 (C-10), 42.89 (C-8), 51.40 (CO_2CH_3), 71.48 (C-12), 174.11 (C-1) and 212.00 (C-9).

To a stirred solution of ester **4** (1.0 g, 3 mmol) in Et_2O (50 cm^3), chromic acid [5 cm^3, prepared from $Na_2Cr_2O_7$ (5 g), conc. H_2SO_4 (7.6 g) and water (15 cm^3)] was added over a period of 15 min and the reaction mixture stirred at ambient temperature for a further 15 min. The ethereal fraction was successively washed with water (20 cm^3), aqueous $NaHCO_3$ (10%, 30 cm^3) and dried (Na_2SO_4). The filtrate was evaporated and the residue recrystallized from light petroleum (bp 40–60 °C) to give methyl 9,12-dioxostearate **5** as white crystals (0.85 g, 85%), mp 50–51 °C; ν_{max}/cm^{-1} 2920, 2860, 1740, 1710, 1460, 1440, 970 and 760; $\delta_H(CDCl_3)$ 0.88 (t, *J* 7.0, 3H, C*H*$_3$), 1.2–1.6 (m, 18H), 2.30 (t, *J* 7.0, 3H, 2-*H*), 2.40 (t, *J* 6.8, 4H, 8-*H*, 13-*H*), 2.67 (s, 4H, 10-*H*, 11-*H*) and 3.66 (s, 3H, CO_2CH_3); $\delta_C(CDCl_3)$ 14.01 (C-18), 22.48 (C-17), 23.78/23.89 (C-7/C-14), 24.92 (C-3), 28.65–29.50, 31.58 (C-16), 34.07 (C-2), 36.08 (C-10, C-11), 42.79/42.90 (C-8/C-13), 51.35 (CO_2CH_3), 173.73 (C-1) and 209.65 (C-9, C-12).

General procedure for synthesis of the pyridazines 6a–d as exemplified by the reaction of compound 5 with methyl hydrazine

A mixture of methyl 9,12-dioxostearate (0.5 g, 1.5 mmol), water (30 cm^3) and alumina (3 g, Merck art. 1078) was cooled to 0–5 °C. Methyl hydrazine (0.14 g, 3 mmol) was added dropwise to the reaction mixture. The reaction mixture was sonicated for 15 min in an ice bath and then extracted with Et_2O (3 × 30 cm^3). The combined ethereal extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated to give crude compound **6b**. This, when subjected to preparative thin layer chromatographic separation on silica gel using hexane–Et_2O (3 : 2 v/v) as developer, gave compound **6b** (0.49 g, 80%); ν_{max}/cm^{-1} 2920, 2860, 1740, 1585, 1430, 1230 and 710; $\delta_H(CDCl_3)$ 0.89 (t, 3H, C*H*$_3$), 1.2–1.8 (m, 18H, C*H*$_2$), 2.32 (t, *J* 7.0, 2H, 2-*H*), 2.79 (t, *J* 7.5, 2H), 2.60 (t, *J* 7.5, 2H), 4.09 (s, 3H, N^+-C*H*$_3$), 3.66 (s, 3H, CO_2CH_3) and 6.59 (s, 2H, ring C-*H*); $\delta_C(CDCl_3)$ 14.04/14.08, 22.51/22.58, 24.20/24.29, 24.86/24.87, 29.02–29.70, 31.63, 34.04/34.07, 39.81 (N^+-CH_3), 51.46 (CO_2CH_3), 109.52 (C-10, C-11), 151.47/151.64, 191.98/192.12 and 174.25/174.29 (C-1) (Found: M^+, 335.5444. $C_{20}H_{35}N_2O_2$ requires *M*, 335.5432).

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