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

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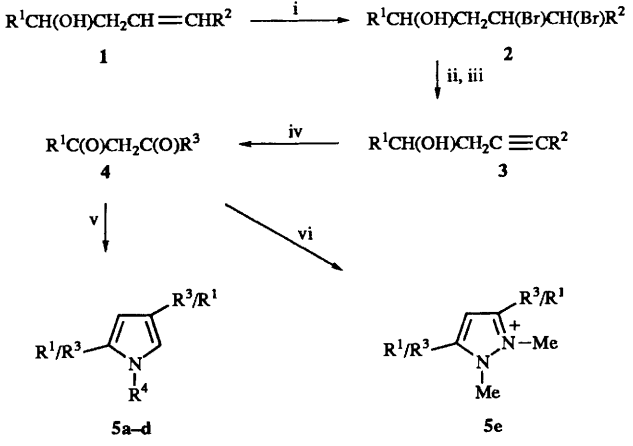
Reactions induced by ultrasonic irradiation of methyl 10,12-dioxostearate with hydrazines in water at 60 °C provide high yields of pyrazole fatty esters.

Pyrazoles have attracted attention because of their bacteriostatic, bacteriocidal and fungicidal properties[1,2] and steroidal compounds which contain this heterocyclic ring have potential as psychopharmacological agents.[3] Practically all linear 1,3-diketones give the corresponding pyrazole derivatives with hydrazines when the reaction is carried out in ethanolic solutions[4,5] or on alumina or clay without solvent.[6]

Since long-chain fatty esters (LCFEs) are insoluble in water most of their reactions are performed in suitable organic solvents. However, we have discovered that when induced by ultrasonic irradiation (20 KHz, 53 W/cm^2) LCFEs undergo successful reactions in water.[7] Here we describe high-yielding reactions involving methyl 10,12-dioxostearate **4** and hydrazines. Compound **4** was obtained by bromination of methyl ricinoleate [methyl (*Z*)-12-hydroxyoctadec-9-enoate, **1**] followed by ultrasound-assisted dehydrobromination of the 9,10-dibromo-12-hydroxy intermediate **2** with ethanolic KOH to give 12-hydroxyoctadec-9-ynoic acid **3**, the methyl ester of which undergoes oxidation, induced by ultrasonic irradiation, with chromic acid in water (**4**, 65%; see Scheme 1).

In contrast to the unsuccessful reactions of compound **4** with the hydrazines **6a–e** in water in the absence of ultrasonic irradiation (3 days at ambient temperature with stirring or under reflux for 4 h) similar reactions in its presence (20 KHz, 53 W cm^{-2}) at room temperature (24 °C) for 8–10 min gave *ca.* 40–50% yield of the corresponding pyrazole fatty esters **5a–e** (Table 1; reactions I). Further, reactions carried out at 60 °C were complete within 7–10 min and gave product yields of 75–90% after purification (Table 1; reactions II). Product identification was established on the basis of spectral results [high resolution molecular ion mass (M^+) and ^{1}H and ^{13}C NMR].

During sonication of the reaction mixture, the insoluble fatty ester substrate is homogenized, the hydrazines being water insoluble apart from **6a** and **6b**. 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.[8]



R^1 = $Me(CH_2)_5$, R^2 = $MeO_2C(CH_2)_7$, R^3 = $MeO_2C(CH_2)_8$,

R^4 = H, Me, Ph or $C_6H_4NO_2$

Scheme 1 *Reagents and conditions:* i, Br_2, Et_2O; ii, KOH, EtOH, ultrasound; iii, BF_3–MeOH; iv, chromic acid, water, ultrasound; v, R^4NHNH_2 **6**, H_2O, ultrasound; vi, MeNHNHMe, water, ultrasound

Table 1

		Reactions I		Reactions II	
Product	R^4	time (min)	yield (%)	time (min)	yield (%)
5a	H	8	48	7	90
5b	Me	8	45	7	82
5c	Ph	10	45	10	90
5d	$C_6H_4NO_2$	10	42	10	75
5e	—	8	40	7	79

Experimental

Preparation of methyl 10,12-dioxostearate 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** (3.0 g, 99%) as a viscous liquid. 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, Undatim Ultrasonics S.A., Louvain-la-Neuve, Belgium), at ambient temperature. The reaction mixture was acidified with HCl (6 mol dm^{-3}; 20 cm^3) and extracted with Et_2O (2 × 30 cm^3). The combined extracts were washed with water (2 × 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 × 50 cm^3). The combined extracts were evaporated and silica column chromatographic purific-

ation 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%). A mixture of the ester **3** (1.3 g, 4.2 mmol), water (20 cm^3) and chromic acid [20 cm^3; prepared from $Na_2Cr_2O_7$ (5 g), conc. H_2SO_4 (7.6 g) and water (15 cm^3)] was sonicated for 6 min at ambient temperature. The ethereal extract was washed with aqueous $NaHCO_3$ (10%; 20 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and evaporated to give pure methyl 10,12-dioxostearate **4** (1.3 g, 95%).

General procedure for synthesis of the pyrazoles 5a–e as exemplified by the reaction of compound 4 with hydrazine

A mixture of methyl 10,12-dioxostearate (100 mg, 0.3 mmol), hydrazine hydrate (70 mg, 1.4 mmol) and water (20 cm^3) was sonicated at 60 °C for 8 min, after which it was extracted with Et_2O (2 × 20 cm^3). The combined extracts were washed with brine (20 cm^3), dried (Na_2SO_4) and evaporated to give crude compound **5a**. This, when subjected to preparative thin layer chromatographic separation on silica gel using hexane–Et_2O (1:1, v/v) as developer gave compound **5a** (96 mg, 90%).

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