Convenient Thionation of Triglycerides with Lawesson's Reagent

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ABSTRACT: Thionation using the Lawesson's reagent (LR) led to quantitative and selective replacement of carbonyl groups (C=O) with thionocarbonyl groups (C=S). Mixtures of thionotriglycerides were obtained by reaction of 2,4-bis (*p*-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide in suspension with triglycerides (TG). With a molar ratio (LR)/(TG) = 3:2, there was complete exchange of C=O with C=S in the carboxylic groups of the TG. The yield is over 90%. The two P=S ligands in the LR confer a double reactivity, producing a high power of thionation. Fourier transform infrared spectroscopy was employed for quantitative and qualitative characterization of the thionated TG and for monitoring the progress of partial or total thionation as conditioned by the molar ratios of the starting compounds. Thus, with molar ratio LR/TG of 0.108, 0.36, and 0.72, we obtained around 6, 20, and 40% of C=O conversion, respectively.

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KEY WORDS: Infrared spectroscopy, Lawesson's reagent, thionation, thionoesters, thionotriglycerides, triglycerides.

Barrett and Lee (1) have described the thionation of esters or lactones using the Belleau reagent (Fig. 1). Moderate yields were obtained in a solvent medium, and the reaction was selective, but not quantitative. Other reagents have been used such as P_2S_5 ... (2), but one of the best agents of thionation is Lawesson's reagent (LR) (Fig. 1). 2,4-Bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide has been found to lead to a high conversion of carbonyl into thionocarbonyl groups in the synthesis of thiocarboxylic *O*-esters. The review of Jones and Bradshaw (3) describes the selective thionation of simple aliphatic and aromatic esters and polyfunctional lactones into the corresponding thionoesters or thionolactones under mild conditions by refluxing in toluene or xylene.

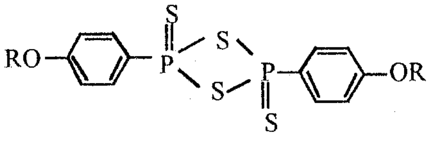

FIG. 1. Lawesson's reagent (LR), (R = CH_3) and Belleau reagent (R =

However, thionated esters have seen relatively few developments, although they have been employed as intermediates in the syntheses of ethers (3,4), alkanes (4), and dithioesters (4). In the glycosidation of oligosaccharides, the thionoesters obtained with the Belleau reagent are key intermediates for stereoselective synthesis of the 1,6-disaccharides (1). The thionoesters can also be used as substrates of some cysteine proteases such as papain (5). We have described an original method for synthesis of 3,6-dialkyl-1,2,4,5-dihydrotetrazines from esters of simple fatty acids and triglycerides (TG) of vegetable oils *via* the thiocarboxylic *O*-esters or *O,O,O*-glyceryl thiocarboxylate (6,7) obtained by replacement of the C=O groups with C=S groups using LR. The dihydrotetrazines show promise as oxygen-fixing agents (7,8), and have anticorrosion properties. In a comparison of the biological properties of the thionoesters with those of the corresponding esters, we noted high antifungal activity of the *O*-ethyl thionooleates (8) (IC_{80} = 9 mg/mL on some resistant strains of *Candida albicans*). The corresponding ester was devoid of activity.

In further comparative studies of fatty esters and thionoesters in lubrication applications, we found that the thionotriglycerides (TTG) derived by thionation of vegetable oils with LR are endowed with anti-wear properties (8). In view of current concerns about the environment, vegetable oils show promise in lubrication in view of their biodegradability and renewable nature. The corresponding TTG are also ecologically acceptable. Remember, the C(=S)–O linkage is encountered in the breakdown products of the decomposition of peptides by the cysteine proteases (5).

In the course of these studies, we investigated the behavior of LR. Its power of thionation was evaluated by determining the amount of reagent required for total and partial thionation. An additional objective was to reduce the quantity of the sulfur reagent LR due to its high cost. This would in turn reduce manufacturing costs of lubricants and additives based on plant oils. We employed Fourier transform infrared spectroscopy (FTIR) for quantitative analysis of the partial and total thionation reactions. The degree of thionation could be reliably determined after establishing a standard curve with corresponding confidence intervals.

EXPERIMENTAL PROCEDURES

Raw materials. The crambe oil used in these experiments was provided by the Coopérative 110 Bourgogne (Chatillon,

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France). The TG had the following fatty acid composition: palmitic acid (16:0) = 1.6%; stearic acid (18:0) = 0.6%; oleic acid (18:1) = 12.2%; linoleic acid (18:2) = 8.8%; linolenic acid (18:3) = 6.6%; arachidic acid (20:0) = 4,4%; behenic acid (22:0) = 2%; erucic acid (22:1) = 57%; docosadienoic acid (22:2) = 0.9%. LR, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (empirical formula $C_{14}H_{14}O_2P_2S_4$, MW = 404.46) was purchased from Aldrich (St. Quentin Fallavier, France).

Total thionation of TG. The reactants were crambe oil (TG) and LR. The reaction of thionation was carried out without solvent in a 250-mL reactor equipped with mechanical stirrer and cooling system at a lab scale. The reaction was conducted under a stream of nitrogen at 150°C for different reaction times, and the experiment was conducted in a fume hood. Preliminary experiments were conducted with 0.36 mol of LR (145 g) for 0.1 mol of TG (98 g).The yield was 99%. After optimization, these proportions were altered to 0.15 mol of LR (60.6 g) for 0.1 mol of TG (98 g). The yield was then over 90%. At the end of the reaction, the mixture was cooled, and the excess LR and its oxygenated by-product were removed by centrifugation. A dark viscous oil was recovered. No more purification was done.

Total TTG. Nuclear magnetic resonance (NMR) ^1H: spectrometer Bruker AC200 (Wissenbourg, France), 200 MHz, solution at 20% vol/vol in $CDCl_3$. The multiplicity of the bands is difficult to determine due to the presence of sulfur and tends to be spread out: 5.35 (6 H, C=C), 3.83 (4 H, CH_2 α and α'), 2.27 [6 H + 1 H, CH_2 (2) and CH β], 1.93 [12 H, CH_2 ($-CH_2-CH=CH-$)], 1.57 [6 H, CH_2 (3)], 1.19 (other H, CH_2), 0.84 (9 H).

NMR ^{13}C: spectrometer Bruker AC200, 50 MHz, solution at 20% vol/vol in $CDCl_3$. 14.18 [CH_3 (18)], 22.75 [CH_2 (17)], 24.92 [CH_2 (3)], 27.26 [CH_2 ($-CH_2-CH=CH-$)], [28.63, 28.93, 29.23, 29.37, 29.55, 29.72 (other CH_2)], 31.96 [CH_2 (16)], 34.1 [CH_2 (2)], [62.15, 65.92 (CH_2 α and α')], 69.49 [CH (β)], [129.79, 130.91 (C=C)] 224.67 (C=S).

Mass spectroscopy: apparatus Nermag R1010 (Argenteuil, France) by chemical ionization with NH_3. m/z = 1015 ($M + NH_4^+$).

Infrared: FTIR PerkinElmer Model 1600 (Courteboeuf, France), pure KBr slabs. 3009.8 [ν (C=C)], [2926.3, 2852.9, (ν (C–H) of CH_2 and CH_3)], 1282.5 [ν (C=S)], 1121.8 cm^{-1} [ν (C–O–C)].

Partial thionation of TG. Partial thionation was carried out using the same procedure as above except with different proportions of reactants. For a 6% thionation: 1 mol of TG for 0.108 mol of LR. For a 20% thionation: 1 mol of TG for 0.36 mol of LR. For a 40% thionation: 1 mol of TG for 0.72 mol of LR.

Thin-layer chromatography (TLC) analyses. In a preliminary study, the reaction of thionated was followed by TLC; the plates were of 0.2 mm aluminum of silica gel 60 F254 (Merck, Darmstadt, Germany). The solvent was composed of hexane/ether diethyl (80:20, vol/vol) which gave for TG $R_f = 0.80$ and for thionated TG $R_f = 0.4$.

Analytical study by FTIR. Standards and test solutions were made up in chloroform at a concentration of 0.04 mol/L. Spectra were recorded in sealed quartz cuvettes in a Perkin-Elmer Model 1600 FTIR spectrometer. The aim was to follow the disappearance of the ν (C=O) band at 1746 cm^{-1}.

Beer-Lambert's law gives the relationship between the absorption and the concentration of the solute: $A = \varepsilon lC$ where A is the absorbance, ε the molar absorption coefficient of the solution, l the optical pathlength cuvette, C the concentration of the solute [ε and l being constants, the plot of $A = f(C)$ is a straight line]. The transmittance is obtained from the infrared (IR) spectrum: $A = \log (T1/T2)$, where $T1$ is the transmittance at the base of the band, $T2$ is the transmittance at the top of the band. The calibration curve is a straight line of equation: $y = 0.0027\, y + 0.0104$ with a coefficient of correlation $R^2 = 0.988$, which is indicative of a linear relationship.

The reliability of the results was based on determination of the intervals of confidence of the values determined from the calibration curve. The aim was to determine an interval of confidence around an obtained value X_0 with a probability $1 - a$ where a is the risk estimated by the operator. Under our conditions, the risk was evaluated at 5%. Use of the calibration equation $y = ax + b + e(x)$ is based on the following conditions: the concentrations of the standard solutions are accurate, the linearity is based on the correlation coefficient, the error is assumed to be constant over the area studied. The data encompass this confidence interval: $X_0 - \sigma_{xo} \cdot t\,(1 - a/2) < X_0 < X_0 + \sigma_{xo} \cdot t\,(1 - a/2)$, where σ_{xo} is the variance of the estimation of X_o. The set of these calculations provides the confidence interval for the measured values $Cx - 3\% < Cx$ (%

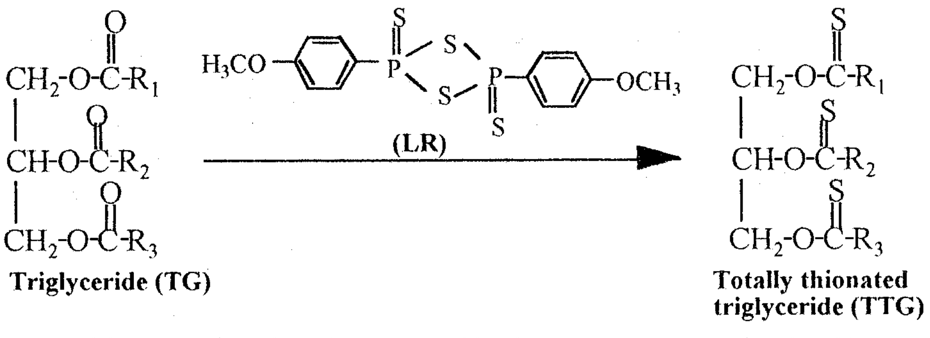

FIG. 2. Total thionation of a triglyceride (TG) (vegetable oil) using LR. See Figure 1 for other abbreviation.

thionated crambe oil) < $Cx + 3\%$).

RESULTS AND DISCUSSION

The reaction of thionation on vegetable oils (TG) in the presence of LR is an exchange of C=O with C=S (Fig. 2). The total TTG are produced, although partially thionated TG (PTTG) can also be formed by suitable choice of the proportions of the reactants.

Study of the progress of the reaction and the efficiency of the LR on these complex esters required a method for assay of the thionated esters. Although it is difficult to assay these molecules individually (TG and PTTG), the proportion of C=O transformed into C=S can be readily determined by IR spectroscopy (Fig. 3). Two characteristic bands are observed in these spectra. On the spectrum of Figure 3A, the ν(C=O) band absorbs at 1746 cm^{-1}. In the spectrum of Figure 3B, this band is replaced by the ν(C=S) band between 1,000 and 1,200 cm^{-1}. In this latter case, the spectrum becomes complex and the ν(C=S) band is superimposed on other absorption bands.

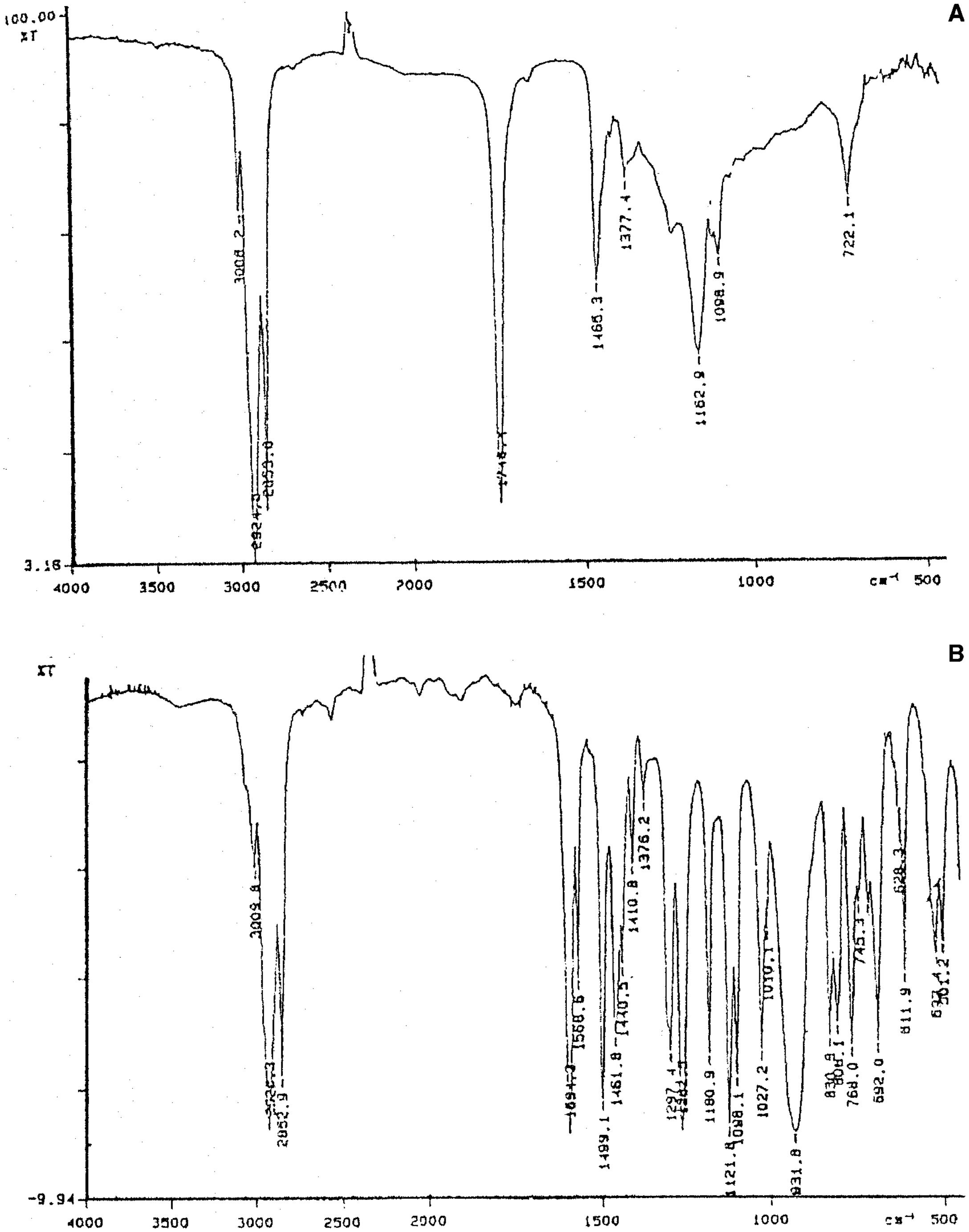

FIG. 3. Infrared spectra of vegetable oil (A) and the totally thionated TG (B). See Figure 2 for abbreviation.

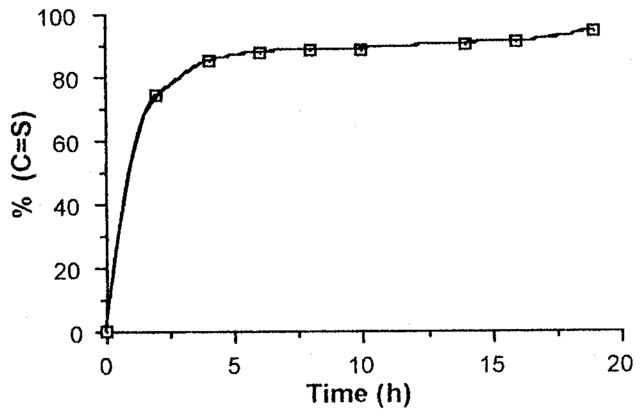

FIG. 4. Progress of the thionation reaction on crambe oil with LR/(C=O) = 0.5. See Figure 1 for abbreviation.

We thus chose to monitor the disappearance of the ν(C=O) band rather than the appearance of the ν(C=S) band. The ν(C=S) band may be contaminated by the ν(C–O) stretching band at 1,150 cm^{-1} and the absorption band of chloroform (solvent) at 1,200 cm^{-1}. The ν(C=O) absorption band is, however, free from interference. Furthermore, since thionation with LR is selective (9), no side reactions occur. The progress of the reaction is readily determined from the calibration curve described in the Experimental Procedures section. The objective was to optimize the amount of LR and to reduce the overall cost of the process.

Encouraged by our previous results, we carried out a systematic study of the utilization of LR in order to determine the optimal experimental conditions for partial and total thionation of vegetable oil TG. In a preliminary study (6), we were able to obtain total thionation (monitored by TLC) with 3.6 mol of LR for 1 mol of TG. In the light of the mechanism of the thionation by LR, we conducted reactions with nonstoichiometric ratios of reactants. Thus, a reaction with a 1.5 mol of LR for 1 mol of TG or a LR/(C=O) ratio = 0.5 produced over 90% of thionated product. Figure 4 illustrates the course of the C=O/C=S exchange reaction in the TG carboxylic groups. It can be seen that the thionation is rapid, nearly quantitative, and regioselective.

We were also able to carry out a partial thionation based on these findings. With molar ratios LR/TG of 0.108 (3%), 0.36 (10%), and 0.72 (20%), we obtained around 6, 20, and 40% thionated oils, respectively. We obtained confidence intervals for the degree of thionation of: 5% < HCRT 6 < 11%, 17% < HCRT 20 < 23%, and 37% < HCRT 40 < 43%. These excellent results indicated that the LR exhibited a double reactivity, interpreted along the lines of a Wittig reaction (10) as proposed by Oae (11) for the reaction of *O,O*-diethyldithiophosphoric acid on carbonyl derivatives. A similar mechanism is illustrated in Figure 5. The thionation power stems from the P=S linkage, and LR can generate a phosphorus ylide and an oxaphosphetane. This system then rapidly decomposes to give the thionotriglyceride and a by-product. After a first reaction as shown in Figure 5, the same reaction takes place at the second site. The position of the C=S groups is randomly distributed within the TG. However, thanks to ^{1}H NMR, we identified that the Hα and Hα' are first modified. The peak shifted from δ = 4.23 ppm (oxygenated TG) to δ = 3.83 ppm (thionated TG). The main reason is the steric hin-

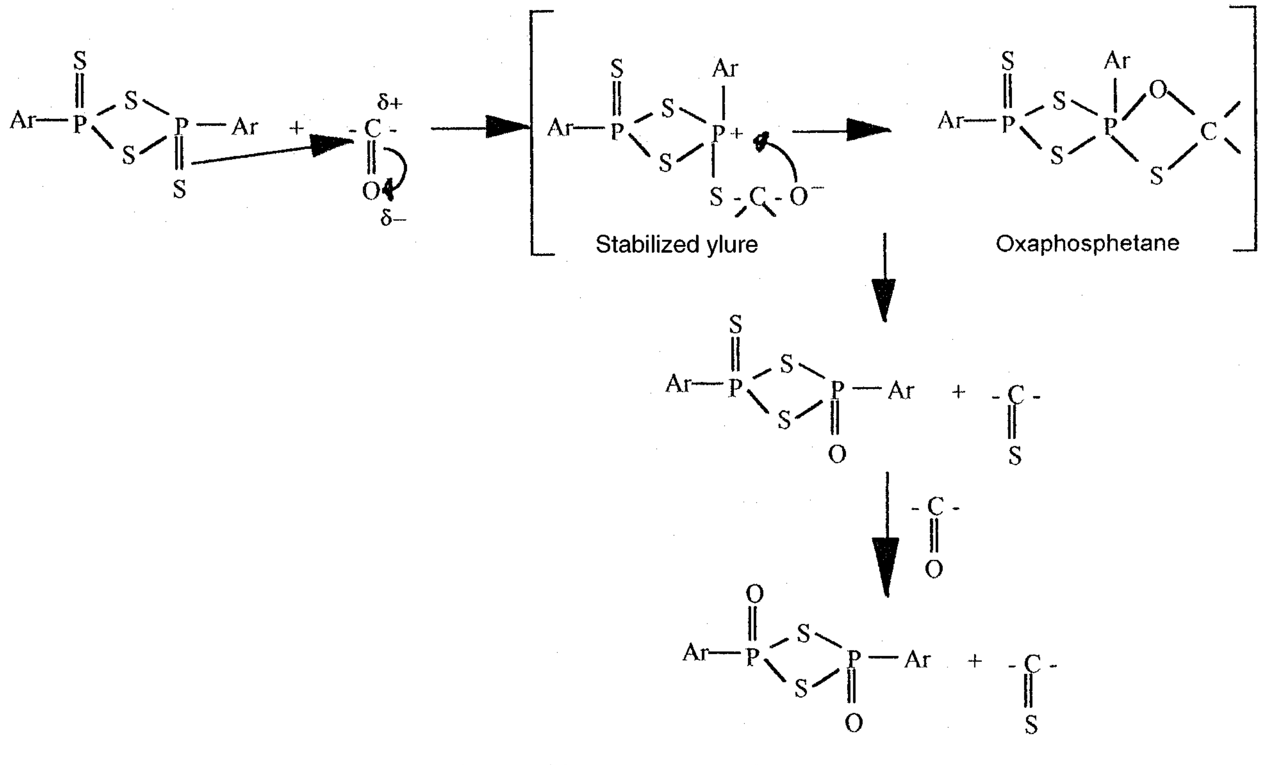

FIG. 5. Mechanism of thionation as a typical Wittig reaction.

drance in position β, but it is not enough to stop the thionation in this position. Thionation of the TG with LR occurs readily due to the high reactivity of its Lewis groups. Both reactive sites on LR were shown to have good reactivity, enabling its use in half-stoichiometric ratios. Depending on the nature of the desired product, partial or total thionation can be obtained using different ratios of reactants. The insertion of a sulfur atom in vegetable oils provides a route to a new range of compounds. The TTG can be employed directly as lubricant additives or as synthetic intermediates. Study of their chemistry and applications is in progress in our laboratory.

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