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Solvent-free thionation of γ -lactones under microwave irradiation

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Abstract—A series of γ -thionolactones was synthesized, with good yields, using a new combination of Lawesson's reagent (LR) and hexamethyldisiloxane (HMDO) in solvent-free conditions under microwave irradiation. © 2003 Elsevier Ltd. All rights reserved.

Most methods developed for the chemical preparation of thionoesters and thionolactones involve an oxygensulfur exchange from the corresponding carbonyl compounds, and usually proceed from thermal processes. Resulting from the pioneering work of Lawesson and co-workers,^{1,2} 2,4-bis(4-methoxy-phenyl)-1,3-dithia-2,4diphosphetane 2,4-disulfide known as Lawesson's reagent (LR), was designed to perform, in defined conditions, a single sulfurization of lactones a selectively resulting in the corresponding thionolactones **b**. Since standard procedures require the use of dry aromatic hydrocarbon solvents and lengthy reaction times, microwave assistance has been advantageously applied to thionate a wide variety of substrates.^{3–5} Nevertheless, there is, to our knowledge, no report dealing with the synthesis of thiono- and dithioanalogues of simple lactones under microwave irradiation.

We were interested in a procedure which could allow us to easily prepare γ -thionolactones, since such compounds were intermediate materials in a synthetic route to 1,4-sulfanylalcohols.⁶ In contrast with previous studies,⁴ the starting substrates we selected are simple and non coumarinic-type lactones, therefore their ring oxygen atom can undergo an oxygen–sulfur exchange. Even though LR shows a remarkable selectivity under standard conditions (dry toluene/xylene, inert atmosphere, 0.5 molar equiv.), it is somewhat less selective under solvent-free and non-homogeneous conditions (heterogeneous phase, unstirred reaction mixture and non-focused microwave irradiation), and provides some of the dithioderivative **d** and some of the thioderivative **c** at trace levels (Fig. 1).

As a suitable model reaction to study the process, we selected the synthesis of γ -thionododecalactone from γ -dodecalactone. All the experiments were run in sealed vessel using an unmodified household microwave oven, by direct exposure of the reaction mixture to microwave irradiation, and working under continuous irradiation at the maximum wattage (850 W). A sequential irradiating process was used, since it was necessary to stir the reaction mixture between irradiation periods of 30 s duration each. In order to calculate



Figure 1. Synthesis of sulfurized γ -lactones using Lawesson's reagent under microwave irradiation.

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the conversion, all the experiments were run twice, with and without hexadecane (0.1 molar equiv.) used as an internal standard. All results are summarized in Table 1.

Initial trials using γ -dodecalactone (5 mmol) and 0.5 equiv. of LR (2.5 mmol) under inert atmosphere were unsatisfactory.⁴ After 2 min of irradiation (4×30 s), the reaction was not selective towards the synthesis of **b** and resulted in a mixture of **b**, **c** and **d** with a moderate conversion (80%, entry 1). This can be explained by the

fact that the formed thionolactone **b** competes with the initial lactone as a sulfurization substrate. Consequently, the higher the amount of dithiolactone **d**, the lower the conversion.

Curphey^{7,8} has shown that the addition of hexamethyldisiloxane (HMDO) to phosphorus pentasulfide (P_4S_{10}) increased the selectivity of this thionating agent for the formation of thionolactones. As described for that reagent combination, a mixture of γ -dodecalactone

Table 1	۱.	Synthesis	of	thionolactones	b	and	dithiolactones	d	under	microwave	irradiation
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Entry	Substrate	Reaction conditions ^a	Time ^b (s)	Conversion ^c (%)	Selectivity ^d (%) b / c / d	Yield ^e (%)
1		LR 0.5 eq	4×30	80	87 / 0 / 13	66 (b) 9 (d)
2	"	$P_4S_{10} 0.25 \text{ eq} / HMDO 1.67 \text{ eq}$	5×30	94	86 / 0 / 14	74 (b) 9 (d)
3	"	LR 0.5 eq / HMDO 0.5 eq	4×30	85	99 / 0 / 1	76
4	"	procedure A ^f	5×30	91	99 / 0 / 1	85
5		"	3×30	94	95 / 0 / 5	80
6		n	"	95	99 / 0 / 1	92
7		n	4×30	98	95 / 0 / 5	88
8		η	5×30	95	99 / 0 / 1	90
9		n	"	91	99 / 0 / 1	89
10		n	"	99	98 / 1 / 1	96
11	"	procedure A / multigram synthesis	2×30	93	96 / 0 / 4	88
12		procedure A	5×30	91	94 / 0 / 6	85
13			"	96	94 / 0 / 6	73 ^g
14		n	3×30	91	95 / 0 / 5	65
15		"	5×30	84	29 / 10 / 61	$\frac{17 \ (\mathbf{b})^{16}}{37 \ (\mathbf{d})^{16}}$
16	"	LR 1 eq	"	99	1 / 0 / 99	94
17		procedure A	3×30	81 ^h	-	44
18		"	"	90 ^h	-	15

^a For conditions see experimental section.¹⁵

^b Number of irradiations for a given time; 3×30 indicates 3 irradiations of 30 seconds duration each.

^c Determined by gas chromatography and calculated from hexadecane used as internal standard.

^d Determined by gas chromatography.

^e Isolated yield.

^f Procedure A : LR 0.75 eq / HMDO 0.75 eq.¹⁵

^g Mixture of two diastereomers.

^hConsumption of the initial lactone \neq conversion.

(0.99 g, 5 mmol), HMDO (1.35 g, 1.67 equiv.) and P_4S_{10} (0.56 g, 0.25 equiv.) was irradiated in solventless conditions to provide similar amounts of **b** and **d** (entry 2) as observed for LR (entry 1).

Using HMDO in a system where P_4S_{10} is replaced by Lawesson's reagent allowed us to improve the selectivity of our procedure for the formation of the expected thionolactones **b**. Although an excellent selectivity is observed, the conversion has not reached more than 84% (entry 3). At least 0.75 equiv. of LR/HMDO were required to reach a satisfying conversion (entry 4). As described in previous reports,^{8–10} variable amounts of a bis(trimethylsily))anisylthiophosphonate are present in reaction mixtures. Moreover, irradiating LR and HMDO allowed us to check that this product is not observed when the reaction is carried out in the absence of carbonyl compound.

At the end of the reaction, the internal temperature reached 120°C. In order to check the microwave effect on the system, the reaction was performed (lactone 5 mmol, LR 0.75 equiv., HMDO 0.75 equiv.) with conventional heating at 120°C for 5 min, after which the reaction reached 27% conversion only. In addition, 3 h of reaction were required to reach a similar conversion to that obtained by microwave procedure, with a very good selectivity.

Lawesson's reagent has been described as undergoing a monomer-dimer equilibrium in solution,^{11,12} while the monomer is known to be the reactive species.¹³ In addition, thionation reactions have been rationalized in terms of nucleophilic attack of carbonyl oxygen upon the electrophilic phosphorus of the monomer species. It has been proposed that microwaves accelerate polar transition state reactions,¹⁴ thus our procedure was favourably performed under microwave irradiation.

Thus, the γ -alkyl- γ -lactones were readily converted into their thiono-analogues (entries 4-12) and the expected compounds were isolated in an 80-96% range. Additionally, a multigram synthesis (25 mmol) of γ thionodecalactone was run, and the expected thionolactone **11b** was isolated with an 88% yield (entry 11). This procedure was successfully extended to synthesize thiono-analogues of whisky lactone and cis-jasmone lactone which are representative flavouring lactones. As a result, thionowhisky lactone and cis-jasmone thionolactone were, respectively, obtained with 73% (entry 13) and 65% yields (entry 14). On the other hand, γ -phenyl- γ -butyrolactone strongly tended to produce a higher amount of dithio-analogue (entry 15) due to its ring oxygen atom in benzylic position. Thus, γ -phenyl-dithiobutyrolactone 16d was readily synthesized using 1 molar equiv. of LR only, affording the expected dithiolactone with 94% yield.

δ-Lactones (entries 17) and ε-lactones (entry 18), which usually require higher reaction temperatures than γ -lactones, were submitted to the procedure applied for the γ -lactones, but provided moderate selectivities and low yields. The internal standardization which is used prior to reaction allowed us to check the entire consumption of the initial lactones, which were poorly converted into the expected compounds. Thus, preliminary studies were performed to assess the reactivity of these substrates to our system. δ - and ε -lactones (**17a** and **18a**, respectively) were submitted to reaction with conventional heating, including an internal standardization. The course of the reaction was monitored for 1 h, and this allowed us to check that the reaction provided similar results to those already observed for the microwave procedure. Moreover, δ - and ε -thionolactones were irradiated in the presence of HMDO, and their stability was checked under these conditions.

In conclusion, we have developed a new and useful procedure which seems to be very effective for the synthesis of γ -thionolactones, and can be easily scaled up to larger quantities. The reactivity of the δ - and ϵ -lactones to our procedure is still under investigation, and work is currently in progress to adjust an efficient synthetic procedure for further extension to a wider variety of lactones.

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- 15. **Procedure A**: A mixture of lactone (5 mmol), Lawesson's reagent (1.52 g, 3.75 mmol) and hexamethyldisiloxane (0.61 g, 3.75 mmol) was placed in a Schlenk-type glass tube fitted with a carefully tightened rubber septum under nitrogen atmosphere, and was exposed to microwave irradiation at maximal wattage (850 W), and stirred with a vortex between irradiations of 30" duration each, after which the internal temperature reached $120\pm5^{\circ}$ C. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and adsorbed on silica gel. Thionolactones were purified by column chromatography using a mixture of hexane/Et₂O (9/1) or pentane/Et₂O (9/1) for the most volatile lactones (entries 5 and 6).

16. Analytical data for new compounds.

γ-Phenyl-γ-thionobutyrolactone **15b**: ¹H NMR (200 MHz, CDCl₃): δ 2.28 (1H, ddd, 8.84, 12.76, 18.06 Hz), 2.70 (1H, dddd, 4.55, 6.70, 8.21, 12.76 Hz), 3.14 (1H, ddd, 4.55, 8.84, 18.69 Hz), 3.28 (1H, ddd, 8.34, 9.47, 18.69 Hz), 5.86 (1H, dd, 6.83, 8.47 Hz), 7.30–7.50 (5H, m) ppm. ¹³C NMR (50.28 MHz, CDCl₃): δ 32.38, 44.93, 90.76, 125.77, 128.83, 128.88, 138.01, 221.86 ppm. MS (EI, 70 eV): m/z (%) 51 (12.0), 77 (14.6), 78 (9.1), 91 (27.4), 103 (9.4), 115 (27.2), 117 (100), 118 (24.1), 123 (9.4), 178 (M⁺⁺, 40.9). Elemental analysis for C₁₀H₁₀OS calcd: C, 67.41%; H, 5.62%; S, 17.98%; found: C, 67.22%; H, 5.61%; S, 18.18%. Mp: 44°C.

γ-Phenyl-γ-dithiobutyrolactone **16d**: ¹H NMR (200 MHz, CDCl₃): δ 2.54 (1H, dddd, 6.70, 10.23, 11.25, 12.76 Hz), 2.80 (1H, dddd, 2.94, 5.68, 6.44, 12.75 Hz), 3.08 (1H, ddd, 6.45, 11.25, 17.93 Hz), 3.37 (1H, ddd, 3.04, 6.83, 17.85 Hz), 5.29 (1H, dd, 5.68, 10.23 Hz), 7.30–7.50 (5H, m) ppm. ¹³C NMR (50.28 MHz, CDCl₃): δ 39.67, 52.82, 61.37, 127.51, 128.41, 128.99, 138.12, 245.28 ppm. MS (EI, 70 eV): m/z (%) 51 (11.9), 77 (19.4), 78 (14.3), 91 (26.9), 103 (12.7), 115 (31.0), 117 (100), 118 (23.8), 194 (M^{•+}, 83.4), 195 (10.5). Elemental analysis for C₁₀H₁₀S₂ calcd: C, 61.85%; H, 5.15%; S, 33.00%; found: C, 61.84%; H, 5.23%; S, 33.06%. Mp: 56°C.