SULFUR-CONTAINING HETEROCYCLES: FACILE SYNTHESIS OF 4*H*-1,3-THIAZINES BY THE REACTION OF 3-*N*-ACYLAMINO KETONES WITH LAWESSON'S REAGENT

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Abstract- The treatment of 3-*N*-acylamino ketones with Lawesson's reagent [**LR**: 2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide] afforded the sulfur-containing heterocycles, 4*H*-1,3-thiazines in moderate to good yields, along with the corresponding 3-*N*-thioacylamino ketones.

INTRODUCTION

The 1,3-thiazines are a class of heterocycles that have received considerable attention[1] due to their interesting biological activities.[2] Several reports on the synthesis of 1,3-thiazines have appeared,[1-6] but many of them suffer from somewhat problems; for example with some methods the usage is restricted to synthesizing only the thiazines with a particular functional group such as amino, cyano, or SR, or the starting material is difficult to obtain. 2,4-Bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, commonly known as Lawesson's reagent (**LR**), exhibits a great ability in converting a wide variety of carbonyl compounds into thiocarbonyl compounds.[7] **LR** is also utilized in the synthesis of phosphorus[8] or sulfur-containing heterocycles.[9] Recently, we have reported the novel routes to sulfur-containing heterocyclic compounds such as tetrahydrothiophene-2-imines,[10] tetrahydrothiophene-2-thione,[10] thiazolines,[11] benzothiazines[11] and 2-amino- thiophenes[12] by

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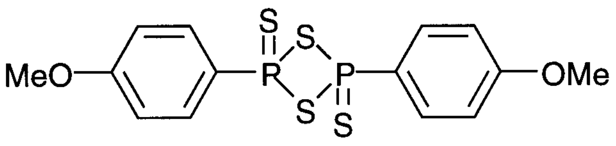
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

the reaction of the substrates containing two functional groups, *e.g.*, ω-hydroxy amides,[10] ω-*N*-acylamino alcohols[11] and ω-keto amides with **LR**.[12] In this communication, we report the simple synthesis of 4*H*-1,3-thiazine derivatives by the reaction of 3-*N*-acylamino ketones with **LR**.

Figure 1. Lawesson's Reagent (**LR**)



RESULTS AND DISCUSSION

The treatment of 3-*N*-acylamino ketones (**1**)[13] with **LR** in toluene at reflux temperature yielded the 4*H*-1,3-thiazine derivatives (**2**) and 3-*N*-thioacylamino ketones (**3**) (Scheme 1).[14] The 4*H*-1,3-thiazine derivatives with various aryl and alkyl groups substituted at the C-2, C-4, and C-6 positions can be easily synthesized by this reaction (Table 1). The structures of the 4*H*-1,3-thiazines (**2**) and 3-*N*-thioacylamino ketones (**3**) were determined based on their spectroscopic data, elemental analyses and chemical evidence. In the ^{1}H-NMR spectrum of the 4*H*-1,3-thiazine (**2c**), the peaks of the methyl protons at C-4 and olefinic proton at C-5 appeared at δ 1.67 and 5.94 as doublets, respectively, indicating the position of the double bond to be between C-5 and C-6 as in Scheme 1. In the ^{13}C-NMR spectrum of the thioamides (**3**), the thioamide carbonyl group exhibited a downfield shift of about 30 ppm compared to the amide carbonyl of **1**, showing that the thionation had occurred at the amide group. The 4*H*-1,3-thiazines (**2a** and **c**) thus obtained were treated with diphenylketene to afford [2+2] cycloadducts, β-lactams (**4a** and **c**), in moderate yields (Scheme 2). The structure of the β-lactams (**4a** and **c**) was characterized by the spectral data and elemental analyses.

Scheme 1

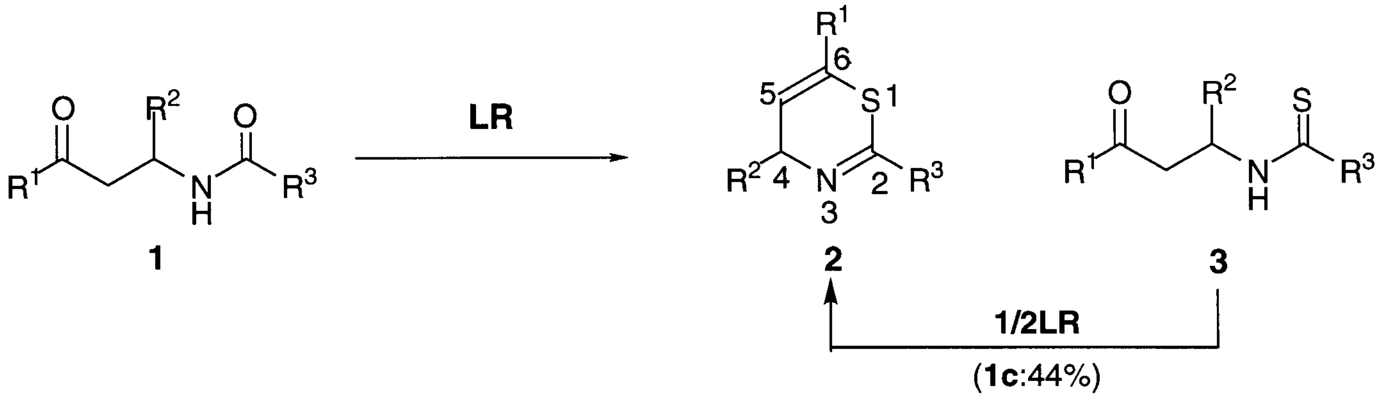
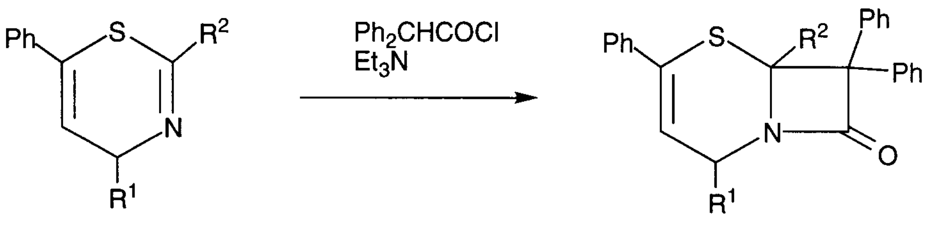


Table 1. Yields of 4*H*-1,3-Thiazines (**2**) and 3-*N*-Thioacylamino Ketones (**3**) in the Reaction of 3-*N*-Acylamino Ketones (**1**) with **LR**[a]

				Molar Ratio	Yield (%)	
	R^1	R^2	R^3	**LR/1**	**2**	**3**
1a	Ph	Ph	*p*-Tol	1	66	26
1a				0.5	11	72
1a[b]					trace	10
1b	*p*-Tol	*p*-Tol	*p*-Tol	1	86	4
1b				0.5	11	79
1c	Ph	Me	Ph	1	11	34
1c				0.5	trace	28
1c[c]				1	31	22
1d	Ph	Ph	*t*-Bu	1	59	trace
1d				0.5	5	16
1e	Ph	Ph	Ph	1	41	27
1e				0.5	12	63
1f	Ph	Ph	*p*-ClC_6H_4	1	52	34
1f				0.5	5	56

[a] Reaction conditions: Reflux in toluene for 15 min. [b] **1a** was refluxed in pyridine for 30 min with 1 eq. of P_4S_{10}. [c] Reflux in toluene for 3 h.

Scheme 2



2a and c **4a and c**

Table 2. Yields of **4** in the Cycloaddition Reaction of 4*H*-1,3-Thiazines (**2a** and **c**) with Diphenylketene

	R^1	R^2	Yield of **4** (%)
2a	Ph	*p*-Tol	41
2c	Me	Ph	50

The yields of the products (**2** and **3**) were dependent on the molar ratio of **LR** to 3-*N*-acylamino ketones (**1**). The 4*H*-1,3-thiazines (**2**) were produced predominantly when an equimolar amount of **LR** was used, while with 0.5 equiv. of **LR** the thioamides (**3**) were mainly produced. The treatment of the thioamide (**3c**) with 0.5 equiv. of **LR** yielded the 4*H*-1,3-thiazine (**2c**) in 44% yield, where no cyclization occurred when refluxing the thioamide (**3c**) in toluene without **LR**. These results suggest that in the reaction of the 3-*N*-acylamino ketones (**1**) with **LR**, the amide group is initially thionated followed by the thionation of the carbonyl group to yield the 3-*N*-thioacylamino thiones, which then gave the 4*H*-1,3-thiazines (**2**) by the cyclization and the elimination of H_2S. In contrast, the treatment of 3-*N*-acylamino ketone (**1a**) with P_4S_{10} resulted in low yield of the thioamide (**3a**) and only a trace of the 4*H*-1,3-thiazine (**2a**).

On the other hand, the treatment of 3-*N*-acylamino esters (**1g-i**) with an equiv. of **LR** gave the 3-*N*-thioacylamino esters (**3g-i**) as the sole product (Scheme 3).[15] This is probably due to the low reactivity of the ester carbonyl group toward **LR**.[7]

Scheme 3

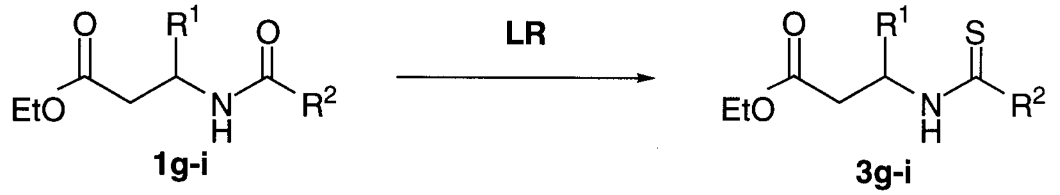


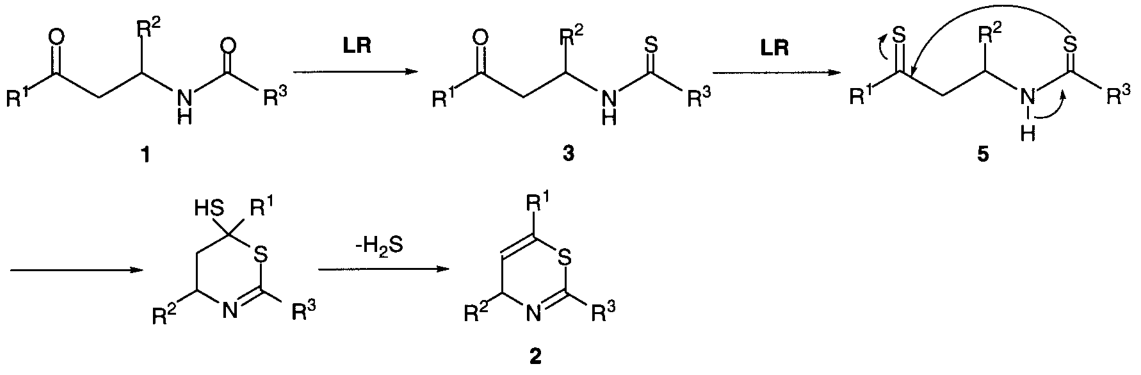
Table 3. Yields of 3-*N*-Thioacylamino Esters (**3**) in the Reaction of 3-*N*-Acylamino Esters (**1g-i**) with **LR**[a]

	R1	R2	Reflux Time (min)	Yield of **3** (%)
1g	Ph	Me	15	94
1h	Me	*p*-Tol	15	78
1i	Ph	*p*-Tol	15	95
1i			300	92

[a] Reaction conditions: Reflux in toluene. Molar ratio: **LR**/**1**=1.

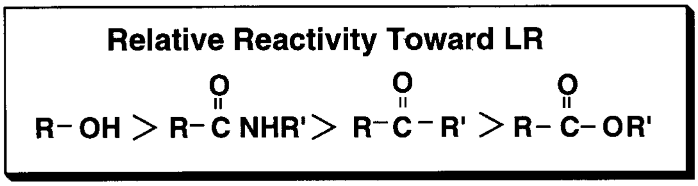
Based on these results, the reaction mechanism for the formation of the 4*H*-1,3-thiazines (**2**) can be explained as shown in Scheme 4. On treatment of 3-*N*-acylamino ketones (**1**) with **LR**, the amide carbonyl group is initially thionated to yield the 3-*N*-thioacylamino ketones (**3**), which then undergoes further thionation of the carbonyl group to form the 3-*N*-thioacylamino thiones (**5**). The subsequent cyclization of **5** with the elimination of hydrogen sulfide yields the 4*H*-1,3-thiazines (**2**).

Scheme 4



It is noteworthy that the amide group seems to be more reactive toward **LR** than the carbonyl group. This tendency has been recently reported by G. Serra *et al.*[16] in the reaction of 2-keto amides with **LR**. On the other hand, we have previously reported that when treating *N*-acylamino alcohols with **LR**, the hydroxy group tends to be more reactive toward **LR** than the amide group.[10,11] Considering from the above findings, the relative reactivity of the functional groups toward **LR** is given below.[17]

Relative Reactivity Toward LR



$$\mathrm{R{-}OH} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}\,NHR'} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R'} > \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'}$$

In conclusion, the procedure described here represents a useful method for the preparation of 4*H*-1,3-thiazines.

REFERENCES AND NOTES

1. H. Quiniou and O. Guillton, ‘Advances in Heterocyclic Chemistry’ , Vol. 50, ed. by A. R. Katritzky, Academic Press, Inc., San Diego, California, 1990, pp. 85-156; M. Sainsburg, ‘Comprehensive Heterocyclic Chemistry’ , Vol. 8, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Inc., Oxford, 1984, pp. 995-1038.
2. J. V. N. Vara Prasad, *J. Heterocycl. Chem.*, 1996, **33**, 1599 and references cited therein.
3. N. Yasuda, M. Karikomi, and T. Toda, *Chem. Lett.*, 1995, 1141.
4. A. J. Liepa and S. Saubern, *Aust. J. Chem.*, 1997, **50**, 755.
5. I. Yamamoto, K. Kajiwara, T. Fujimoto, and K. Ohta, *J. Heterocycl. Chem.*, 1992, **29**, 515.
6. P. Wipf and G. B. Hayes, *Tetrahedron*, 1998, **54**, 6987.
7. M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.
8. B. S. Pederson and S.-O. Lawesson, *Tetrahedron*, 1979, **35**, 2433; A. A. El-Barbary, K.

Clausen, and S.-O. Lawesson, *Tetrahedron*, 1980, **36**, 3309; A. A. El-Barbary and S.-O. Lawesson, *Tetrahedron*, 1981, **37**, 2641; S. Sheibye, S.-O. Lawesson, and C. Romming, *Acta Chem. Scand. B*, 1981, **35**, 239; S. Sheibye, R. Shabana, and S.-O. Lawesson, *Tetrahedron*, 1982, **38**, 993; R. Shabana, F. Osman, and S. S. Atres, *Tetrahedron*, 1994, **50**, 6975; N. Duban-Assibat, A. Baceiredo, and G. Betrand, *J. Org. Chem.*, 1995, **60**, 3904; R. N. Butler, E. C. Makenna, and D. Grogen, *Chem. Commun.*, 1997, 2149.

9. K. Clausen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, 1979, **88**, 305; K. Clausen and S.-O. Lawesson, *Nouv. J. Chim.*, 1980, **4**, 43; A. Ishii, J. Nakayama, M.-X. Ding, N. Kotaka, and M. Hoshino, *J. Org. Chem.*, 1990, **55**, 2421; P. N. Nugara, N.-Z. Huang, M. V. Lakshmikanthan, and M. P. Cava, *Heterocycles*, 1991, **32**, 1559; T. Ozturk, *Tetrahedron Lett.*, 1996, **37**, 2821; K. Kang and J. S. U, *Synth. Commun.*, 1995, **25**, 2647; C. W. Ong, C. M. Chen, L. F. Wang, and P. C. Shieh, *Tetrahedron Lett.*, 1998, **39**, 9191.
10. T. Nishio, *Tetrahedron Lett.*, 1995, **36**, 6113; T. Nishio and H. Sekiguchi, *Tetrahedron*, 1999, **55**, 5017.
11. T. Nishio, *J. Org. Chem.*, 1997, **62**, 1106.
12. T. Nishio, *Helv. Chim. Acta*, 1998, **81**, 1207.
13. The starting material, 3-*N*-acylamino ketones (**1**), can be readily prepared from the corresponding 3-*N*-acylenaminones: A solution of 3-*N*-acylenaminones (3mmol) in ethanol (60ml) was hydrogenated over palladium-charcoal (300mg) for 2.5-7 hr. The usual work-up gave 3-*N*-acylamino ketones (**1**) in 30-95% yields.
14. General procedures for the reaction of 3-*N*-acylamino ketones (**1**) with **LR**:
    A solution of 3-*N*-acylamino ketones (**1**) (2mmol) and **LR** (1-2mmol) in toluene (50ml) was heated to reflux under Ar for 15min. After removal of the solvent, the residual oil was chromatographed on a silica-gel column with toluene/AcOEt 50:1 or toluene/hexane 4:1-1:1 to give products **2** and **3**.
15. The formation of the cyclized products, 1,3-thiazine-6-thiones, in the reaction of *N*-acylenamino esters with **LR** was reported: R. Shabana, J. B. Rasmussen, and S.-O. Lawesson, *Tetrahedron*, 1981, **37**, 1819.
16. G. Serra, G. Mahler, and E. Manta, *Heterocycles*, 1998, **48**, 2035.
17. The similar selectivity of **LR** toward these functional groups was observed in the reaction of a mixture of four substrates (benzhydrol, benzanilide, dibenzyl ketone, and ethyl benzoate) with **LR**: M. Ori and T. Nishio, unpublished results.

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