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THIONATION OF *N*-ACYLTHREONINE AND ITS METHYL ESTER WITH LAWESSON'S REAGENT: SYNTHESIS OF 5-OXAZOLONES, 5-THIAZOLONES AND THIAZOLINES

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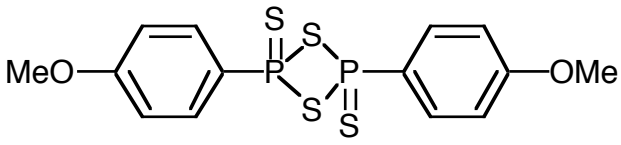
Abstract- The treatment of *N*-acylthreonine (**1**) with Lawesson's reagent [**LR**: 2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide] afforded 5-oxazolones (**2**) in moderate yields, along with 5-thiazolones (**3**). On the other hand, *N*- acylthreonine methyl ester (**5**) reacted with **LR** to give 5-thiazolones (**3**) and 4-methoxycarbonylthiazolines (**6**).

INTRODUCTION

2,4-Bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, commonly known as Lawesson's reagent (**LR**), is utilized as a superior thionation reagent for a wide variety of carbonyl into thiocarbonyl compounds.[1] Several sulfur-[2,3] and phosphorus-containing heterocycles[4] have been synthesized by reacting **LR** with compounds possessing one or several functional groups. Recently we reported the direct conversion of alcohols into thiols by the treatment of alcohols with **LR**,[5] and some sulfur-containing heterocycles were synthesized by treating bifunctional compounds containing a hydroxyl group with **LR**. For instance, tetrahydrothiophene-2-imines,[6] tetrahydrothiophene-2-thiones,[6] thiazolines,[7] and benzothiazines[7] were obtained from the reaction of ω-hydroxy amides[6] and ω-*N*-acylamino alcohols[7] with **LR**. We extended the use of **LR** to multifunctional substrates and here report our results on the reaction of *N*- acylthreonine (**1**) and its methyl ester (**5**) with **LR**.

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



RESULTS AND DISCUSSION

The reaction of *N*-acylthreonine (**1**) with an equimolar amount of **LR** in toluene at reflux temperature afforded 5-oxazolones (**2**) in moderate yields, along with 5-thiazolones (**3**) (Scheme 1, Table 1). Olefins (**4**), a dehydration product of **1**, were isolated as byproducts when the amount of **LR** was dropped to 0.5 equiv. The structures of 5-oxazolones (**2**), 5-thiazolones (**3**) and olefins (**4**) were determined based on their spectroscopic data and elemental analyses. The treatment of olefin (**4a**) with 0.5 equiv. of **LR** yielded 5-oxazolone (**2a**) and 5-thiazolone (**3a**), where no cyclization occurred when olefin (**4a**) was refluxed in toluene without **LR**. Moreover, the treatment of 5-oxazolone (**2a**) with **LR** resulted in the recovery of **2a**, indicating that 5-thiazolones (**3**) are not formed by the thionation of 5-oxazolones (**2**). Therefore, these results suggest that both the cyclized products (**2**) and (**3**) are formed by the treatment of olefins (**4**) with **LR**. The reaction of *N*-acylthreonine (**1**) with P_2S_5 gave similar results to that of **1** with **LR**.

Scheme 1

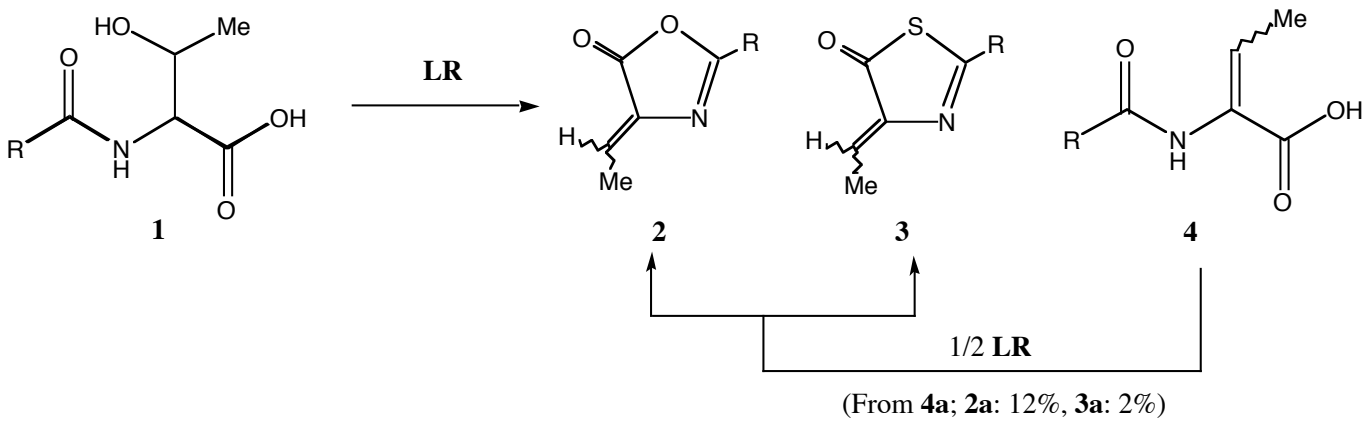


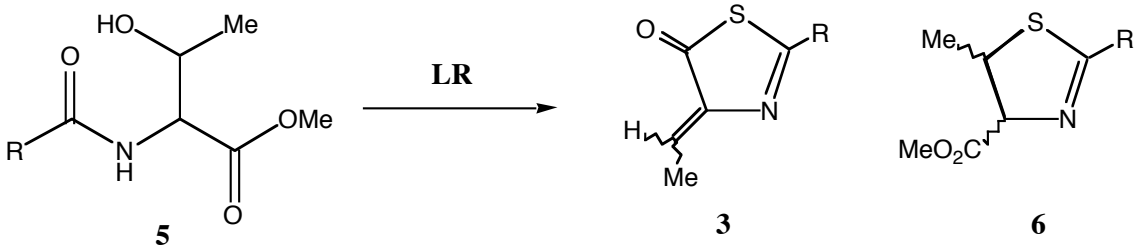
Table 1. Yields of 5-oxazolones (**2**), 5-thiazolones (**3**) and olefins (**4**) in the reaction of *N*-acylthreonine (**1**) with **LR**[a]

		Molar ratio	Yield (%)		
	R	**LR/1**	**2**	**3**	**4**
1a[b]	Ph	1	43	4	11
1a		1	61	trace	-
1a[c]		1	32	18	-
1a		1.5	28[e]	6[e]	-
1a		0.5	30	3	15
1a[d]			41	14	-
1b	*p*-ClC_6H_4	1	41	24	-
1b		0.5	50	15	13
1b[d]			50	16	-
1c	*p*-Tol	1	40	6	-
1c		0.5	39	12	6
1c[d]			63	12	-

[a]Reaction conditions: Reflux in toluene for 2 h. [b]Reflux in toluene for 30 min. [c]Reflux in toluene for 4 h. [d]**1** was refluxed in toluene with 0.4 eq. of P_2S_5 for 2 h. [e]Determined by ^{1}H-NMR.

Consequently, we investigated the reaction of *N*-acylthreonine methyl ester with **LR**. It can be presumed that the methyl ester group does not react with **LR**, due to the low reactivity of the ester carbonyl group toward **LR** that has been previously reported.[1,3] The treatment of *N*-acylthreonine methyl ester (**5**) with an equimolar amount of **LR** afforded the 5-thiazolones (**3**) and 4-methoxycarbonyl thiazolines (**6**) as a mixture of two stereoisomers (*syn*, *anti*) (Scheme 2, Table 2). By measuring the NOE of the thiazoline (**6a**), the main product appeared to have an *anti* configuration; among the 4- and 5- substituents of the thiazoline ring, the NOE between 4-H and the 5-H was not observed (Figure 2). The treatment of **5** with 0.5 eq. of **LR** led to inseparable mixtures, but the formation of the cyclized products **3** and **6** was detected by TLC and HPLC. In contrast, the thiazoline (**6b**) was only obtained when *N*-acylthreonine methyl ester (**5b**) was reacted with P_2S_5.

Scheme 2



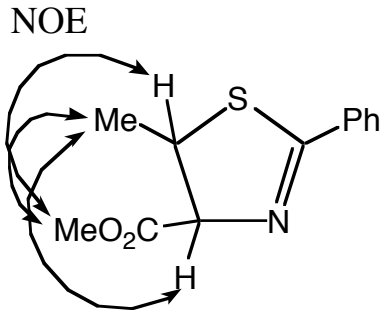
5 **3** **6**

Table 2. Yields of 5-thiazolones (**3**) and 4-methoxycarbonyl thiazolines (**6**) in the reaction of *N*-acylthreonine methyl ester (**5**) with **LR**[a]

		Yield (%)	
	R	**3**	**6** (***anti*:*syn***)[d]
5a	Ph	37	21 (5.4:1)
5a[b]		20	30
5b	*p*-ClC_6H_4	11	37 (9.4:1)
5b[c]		-	26
5c	*p*-Tol	23	37 (4.7:1)

[a]Reaction conditions: Reflux in toluene with 1 eq. of **LR** for 2 h. [b]Reflux in toluene with 1 eq. of **LR** for 4 h. [c]**5b** was refluxed in toluene with 0.4 eq. of P_2S_5 for 2 h. [d]Determined by ^{1}H-NMR.

Figure 2. The NOE measurement of 4-methoxycarbonyl thiazoline (**6a**)

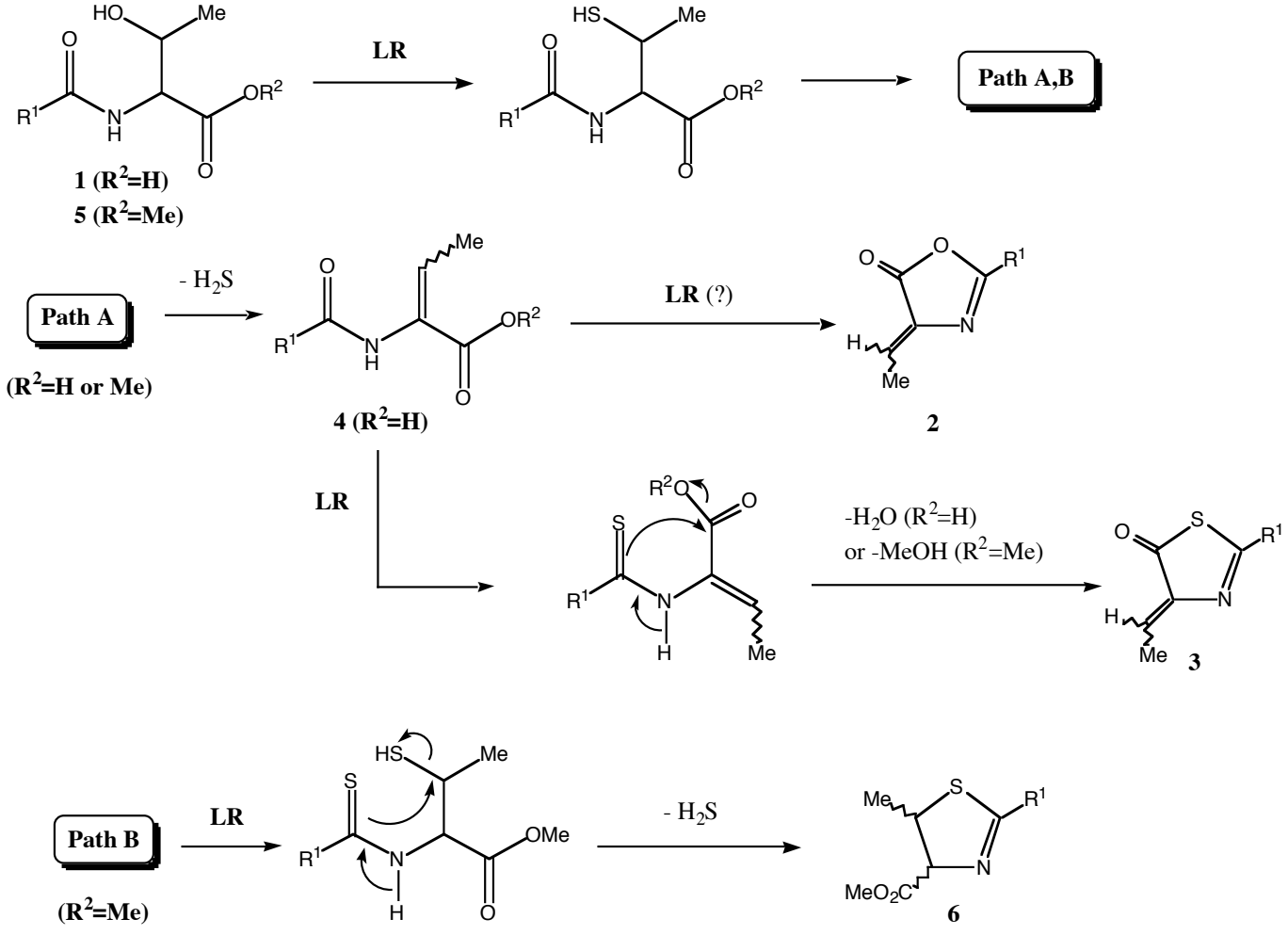


6a

On the basis of these results and our earlier findings,[5,7] the mechanism for the formation of the cyclized products (**2**), (**3**), (**6**) can be explained as shown in Scheme 3. The hydroxyl group of *N*-acylthreonine

derivatives (**1**), (**5**) is initially converted to the corresponding thiol group by **LR**. The olefins (**4**) are formed by the subsequent loss of H_2S, which then undergoes further thionation to form 5-oxazolones (**2**) or 5-thiazolones (**3**) (Path A). On the formation of the 5-thiazolones (**3**), the amide group of the olefins (**4**) are apparently thionated by **LR**, followed by the cyclization with the elimination of H_2O or MeOH. The role of **LR** in the formation of 5-oxazolones (**2**) requires more careful consideration. The pathway B, which involves the formation of thioamide followed by the cyclization, leads to the formation of the thiazolines (**6**). The similar reaction mechanism is proposed in the formation of thiazolines from the reaction of 2-*N*-acylamino alcohols with **LR**.[7]

Scheme 3



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EXPERIMENTAL

Flash column chromatography was carried out with silica gel Wakogel C-300. Melting points and boiling points were determined on a Yanaco micro melting-point apparatus (MP-J3) and a Shibata glass tube oven distillation apparatus (GTO-350RD), respectively, and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 spectrophotometer, in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-EX-270 (270 MHz) or VARIAN GEMINI 200 (200 MHz); measured in $CDCl_3$ unless noted, using TMS as an internal standard; δ values in ppm, *J* values in Hz.

Reaction of *N*-acyl threonine (1) with LR: A solution of *N*-acylthreonine (**1**) (1 mmol) and **LR** (1-0.5 mmol) in toluene (30 mL) was refluxed under argon for 0.5-4 h. After removal of the solvent, the residue was chromatographed with toluene-ethyl acetate (10:0-2:1-0:10) to give products (**2**), (**3**) and (**4**).

4-Ethylidene-2-phenyl-5-oxazolone (2a): mp 89-90℃ ($CHCl_3$-hexane); IR (KBr) 1794, 1675; ^{1}H-NMR δ 2.16 (3H, d, *J*=7.3), 6.66 (1H, q, *J*=7.3), 7.18-7.53 (3H, m), 7.93-8.01 (2H, m); ^{13}C-NMR δ 14.6, 125.6, 128.1, 128.8, 133.0, 134.8, 137.1, 139.3, 162.6, 165.8; HRMS: Calcd for $C_{11}H_9NO_2$ 187.1938. Found 187.0632. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.35; H, 4.98; N, 7.33.

2-(*p*-Chlorophenyl)-4-ethylidene-5-oxazolone (2b): mp 153-155℃ ($CHCl_3$-hexane); IR (KBr) 1794, 1673; ^{1}H-NMR δ 2.25 (3H, d, *J*=7.6), 6.77 (1H, q, *J*=7.6), 7.47 (2H, d, *J*=8.6), 8.02 (2H, d, *J*=8.2); ^{13}C-NMR δ 14.7, 124.1, 129.1, 129.3, 135.5, 136.9, 139.5, 161.8, 165.6. Anal. Calcd for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.28; H, 3.68; N, 6.25.

4-Ethylidene-2-(*p*-tolyl)-5-oxazolone (2c): mp 109-111℃ ($CHCl_3$-hexane); IR (KBr) 1798, 1637; ^{1}H-NMR δ 2.23 (3H, d, *J*=7.8), 2.43 (3H, s), 6.72 (1H, q, *J*=7.8), 7.30 (2H, d, *J*=7.8), 7.98 (2H, d, *J*=7.8); ^{13}C-NMR δ 14.5, 21.8, 122.8, 127.8, 128.1, 129.6, 130.0, 137.1, 138.5, 144.0, 162.8, 166.0. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.31; H, 5.65; N, 6.90.

4-Ethylidene-2-phenyl-5-thiazolone (3a): mp 100-102℃ ($CHCl_3$-hexane); IR (KBr) 1698, 1637; ^{1}H-NMR δ 2.33 (3H, d, *J*=7.6), 6.76 (1H, q, *J*=7.6), 7.26-7.57 (3H, m), 7.93-7.96 (2H, m); ^{13}C-NMR δ 15.5, 127.9, 128.9, 132.4, 133.4, 134.8, 150.9, 165.2, 193.0. Anal. Calcd for $C_{11}H_9NOS$: C, 65.02; H, 4.46; N,

6.89. Found: C, 64.68; H, 4.57; N, 6.73.

2-(*p*-Chlorophenyl)-4-ethylidene-5-thiazolone (3b): mp 102-104℃ ($CHCl_3$-hexane); IR (KBr) 1698, 1635; ^{1}H-NMR δ 2.33 (3H, d, *J*=7.6), 6.78 (1H, q, *J*=7.5), 7.46 (2H, d, *J*=8.4), 7.88 (2H, d, *J*=8.4); ^{13}C-NMR δ 15.6, 129.1, 129.2, 129.3, 131.8, 135.5, 138.6, 150.7, 164.6, 193.0. Anal. Calcd for $C_{11}H_8NOClS$: C, 55.58; H, 3.39; N, 5.89. Found: C, 55.58; H, 3.46; N, 5.82.

4-Ethylidene-2-(*p*-tolyl)-5-thiazolone (3c): mp 75-77℃ ($CHCl_3$-hexane); IR (KBr) 1700, 1636; ^{1}H-NMR δ 2.31 (3H, d, *J*=7.5), 2.43 (3H, s), 6.71 (1H, q, *J*=7.3), 7.28 (2H, d, *J*=7.9), 7.84 (2H, d, *J*=7.9); ^{13}C-NMR δ 15.5, 21.7, 125.9, 127.6, 127.9, 129.6, 130.7, 134.0, 143.2, 150.9, 165.1, 193.4. Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.01; H, 5.22; N, 6.34.

2-Ethylidene-4-oxo-4-phenylbutyric acid (4a): mp 189-191℃ ($CHCl_3$-hexane); IR (KBr) 3220, 1698, 1641; ^{1}H-NMR (CD_3OD-$CDCl_3$) δ 1.85 (3H, d, *J*=6.9), 6.97 (1H, q, *J*=6.9), 7.44-7.58 (3H, m), 7.89-7.92 (2H, m); ^{13}C-NMR (CD_3OD-$CDCl_3$) δ 13.9, 126.7, 127.1, 128.2, 131.6, 133.4, 134.9, 166.2, 166.8; MS *m/z* 205 (M^+) and 105.

4-(*p*-Chlorophenyl)-2-ethylidene-4-oxobutyric acid (4b): mp 224-225℃ ($CHCl_3$-hexane); IR (KBr) 3274, 1698, 1649; ^{1}H-NMR (CD_3OD) δ 1.70 (3H, d, *J*=6.9), 6.86 (1H, q, *J*=6.9), 7.40 (2H, d, *J*=8.6), 7.80 (2H, *J*=8.6); ^{13}C-NMR (CD_3OD) δ 14.8, 129.4, 130.5, 131.1, 134.4, 139.9 168.1 168.8; MS *m/z* 241 and 239 (M^+), and 141 and 139.

2-Ethylidene-4-oxo-4-(*p*-tolyl)butyric acid (4c): mp 208-210℃ ($CHCl_3$-hexane); IR (KBr) 3244, 1697, 1640; ^{1}H-NMR (CD_3OD) δ 1.81 (3H, d, *J*=7.0), 2.40 (3H, s), 6.95 (1H, q, *J*=7.0), 7.30 (2H, d, *J*=8.0), 7.82 (2H, d, *J*=8.0); ^{13}C-NMR (CD_3OD) δ 14.1, 21.5, 128.6, 129.2, 130.1, 132.1, 136.7, 143.8, 165.3, 166.8; MS *m/z* 219 (M^+) and 119.

Reaction of *N*-acylthreonine methyl ester (5) with LR: A solution of *N*-acylthreonine methyl ester (**5**) (1 mmol) and **LR** (1-0.5 mmol) in toluene (30 mL) was refluxed under argon for 2-4 h. After removal of the solvent, the residue was chromatographed with toluene-hexane (2:1) or toluene-ethyl acetate (19:1) to give products (**3**) and (**6**).

4-Methoxycarbonyl-5-methyl-2-phenylthiazoline (6a): bp 195℃ (3 mmHg); IR (film) 1738; ^{1}H-NMR δ 1.54 (3H, d, *J*=6.8), 3.84 (3H, s), 4.26-4.40 (1H, m), 4.94 (1H, d, *J*=6.2), 7.35-7.52 (3H, m), 7.83-7.92 (2H, m); ^{13}C-NMR δ 21.7, 48.3, 52.6, 84.6, 128.4, 128.5, 131.5, 132.8, 170.7, 171.0. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 60.91; H, 5.79; N, 5.90.

2-(*p*-Chlorophenyl)-4-methoxycarbonyl-5-methylthiazoline (6b): bp: 200℃ (3 mmHg); IR (film) 1740; ^{1}H-NMR δ 1.55 (3H, d, *J*=6.6), 3.81 (3H, s), 4.24-4.40 (1H, m), 4.91 (1H, d, *J*=6.3), 7.39 (2H, d, *J*=8.2), 7.79 (2H, d, *J*=8.2); ^{13}C-NMR δ 22.2, 49.3, 53.2, 85.2, 129.2, 130.3, 131.8, 138.2, 170.7, 171.4. Anal. Calcd for $C_{12}H_{12}NO_2ClS$: C, 53.43; H, 4.48; N, 5.19. Found: C, 53.27; H, 4.55; N, 5.19.

4-Methoxycarbonyl-5-methyl-2-(*p*-tolyl)thiazoline (6c): bp 197℃ (3 mmHg); IR (film) 1738; ^{1}H-NMR δ 1.54 (3H, d, *J*=6.8), 2.39 (3H, s), 3.80 (3H, s), 4.24-4.38 (1H, m), 4.91 (1H, d, *J*=6.4), 7.21 (2H, d, *J*=8.2), 7.75 (2H, d, *J*=8.2); ^{13}C-NMR δ 21.5, 21.7, 48.3, 52.7, 84.7, 128.6, 129.2, 130.3, 142.2, 170.0, 171.3. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.28; H, 6.30; N, 5.61.

REFERENCES AND NOTES

1. M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.
2. 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, T. Nishio, *Helv. Chim. Acta*, 1998, **81**, 1207.
3. M. Ori and T. Nishio, *Heterocycles*, 2000, **52**, 111.
4. 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; Y. A. Ibrahim, A. M. Kadry, M. R. Ibrahim, J. N. Lisgarten, B. S. Potter, and R. A. Palmer, *Tetrahedron*, 1999, **55**, 13457.
5. T. Nishio, *J. Chem. Soc., Chem. Commun*., 1989, 205; *J. Chem. Soc., Perkin Trans. 1*, 1993, 1113.
6. T. Nishio, *Tetrahedron Lett*., 1995, **36**, 6113; T. Nishio and H. Sekiguchi, *Tetrahedron*, 1999, **55**, 5017.
7. T. Nishio, *J. Org. Chem*., 1997, **62**, 1106.