Direct α-Lithiation of 4,5-Dihydro-1,3-thiazole-4-carboxylic Acids and Electrophilic Substitution[1]

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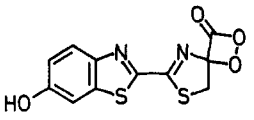
With the aim of developing efficient chemical light systems by way of α-peroxylactones, we have been investigating the mechanism of formation of the α-peroxylactone **1**, which has been postulated[2] as the active intermediate in the firefly luciferin bioluminescence (*Photinus pyralis*). Since the α-hydroperoxyacid **2**, which is in principle accessible through the direct oxygenation[3] of the α-lithiocarboxylate of luciferin, serves as precursor to **1**, we decided to assess the behavior of the readily available[4] luciferin analogs 2-phenyl-4,5-dihydro-1,3-thiazole-4-carboxylic acids **3a,b** towards metalation and electrophilic substitution of the resulting α-lithiocarboxylates.



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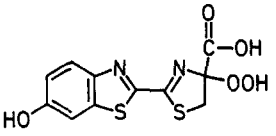

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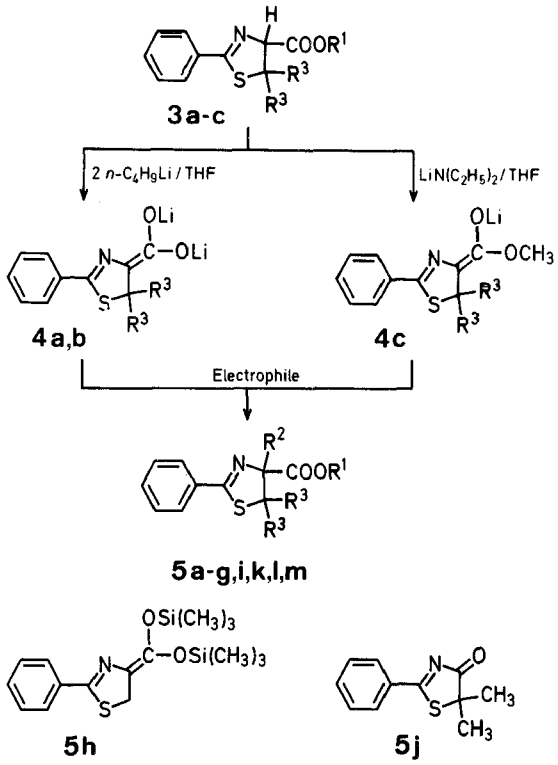
α-Lithiocarboxylates are usually generated by reaction of the carboxylic acids with two moles of lithium diisopropylamide (LDA) at room temperature[5]. Surprisingly, the α-lithiocarboxylate **4a,b** could not be obtained with LDA. However, on slow addition of two moles of butyllithium to a tetrahydrofuran solution of **3a,b**, the two protons could be essentially quantitatively "titrated"[6], leading to a deep red solution. The fact that the butyllithium did not add to the C=N[7] nor the C=O group[8] under these conditions[9] is rather unusual. Subsequent treatment of the lithiocarboxylate with a number of electrophiles afforded the substitution products **5**. In view of the ready hydrolysis and great water solubility (as carboxylate or immonium salt), some of the substitution products **5** were difficult to purify, which resulted in low yields.



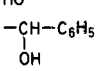
The spectral data confirmed the structure of the substitution products **5**. Thus, the ^{1}H-N.M.R. spectra ($CDCl_3$) showed singlets at $\delta = 3.75$–4.1 ppm, for the protons at the 5-position of **5a**, **e–h**, **k**, **m**, while **5b–d,l** exhibited an AB system with a coupling constant of 11 Hz at $\delta = 3.5$–3.8 ppm and $|\nu_A - \nu_B| = 0.6$–0.45 ppm[10]. For compound **5j**, the two methyl singlets which occurred as distinct resonances in **3b** were overlapped at $\delta = 1.75$ ppm. Also the I.R. spectra of **5j** and its monomethyl derivative[10] were essentially identical.

The intermediacy of the α-hydroperoxy acid of **3b** in the subsequent oxygenation of the dianion solution at −78° was secured by a better than 90% peroxide titer and by the isolation of the 5-oxo compound **5j** upon warm up of the oxygenated reaction mixture. Compound **5j** is presumably formed by Grob fragmentation of the intermediary α-hyroperoxy-acid derived from **3b**. The analogous oxyluciferin could be isolated from the autoxidation of the firefly luciferin, for which the α-hydroperoxyacid **2** and α-peroxylactone **1** have been postulated as intermediates[11].

In conclusion, it is novel that the sensitive 4,5-dihydro-1,3-thiazole-4-carboxylic acids can be directly α-metalated with butyllithium, a fact which offers interesting synthetic possibilities. For example, addition of acid chlorides to the C=N bond should make 2-substituted penicillines readily available[12].

As an example, the synthesis of **5e** is described below (**5a–m**, see Table).

Table. Starting Materials (**3**), Electrophiles, Yields (not optimized), and Melting Points of Electrophilic Substitution Products **5**

Educt	Electrophile	Product	R^1	R^2	R^3	Yield [%]	m.p.	Molecular formula[a]
3a	D_2O	**5a**	H	D	H	88	114–118°	$C_{10}H_8DNO_2S$ (208.3)
3a	Oxygen ($^3O_2$)	**5b**[b]	H	OH	H	55	oil	
3a	Iodomethane	**5c**	H	CH_3	H	90	184–188°[c]	$C_{11}H_{11}NO_2S \cdot HCl$ (257.7)
3a	Benzyl bromide	**5d**	H	$CH_2—C_6H_5$	H	89	186–190°[c]	$C_{17}H_{15}NO_2S \cdot HCl$ (333.8)
3a	Acetone	**5e**	H		H	85	158–160°[d]	$C_{13}H_{15}NO_3S$ (265.3)
3a	Cyclohexanone	**5f**	H		H	80	149–151°[d]	$C_{16}H_{19}NO_3S$ (305.4)
3a	Benzaldehyde	**5g**	H		H	48	150–151.5°	$C_{17}H_{15}NO_3S$ (313.4)
3a	Chlorotrimethylsilane	**5h**[e]	—	—	H	80	oil	
3b	D_2O	**5i**	H	D	CH_3	82	123–125°	$C_{12}H_{12}DNO_2S$ (236.3)
3b	Oxygen ($^3O_2$)	**5j**	—	—	CH_3	80	oil	
3c	D_2O	**5k**	CH_3	D	H	95	64–67°	$C_{11}H_{10}DNO_2S$ (222.3)
3c	Oxygen ($^3O_2$)	**5l**	CH_3	OH	H	60[f]	148–151°[d]	$C_{11}H_{11}NO_3S$ (238.3)
3c	Ethyl carbonochloridate (Cl—$COOC_2H_5$)	**5m**	CH_3	$COOC_2H_5$	H	90	41–43°	$C_{14}H_{15}NO_4S$ (293.3)

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.64%, H ±0.35%, N ±0.47%).

[b] The α-hydroxy compound is unstable and decomposes to the 1,3-thiazole derivative besides other products.

[c] Hydrochloride, melts with decomposition.

[d] Decomposition.

[e] The possibility of hydrolysis and the high boiling point of **5h** did not allow purification. The ^{1}H-N.M.R. spectrum shows a 90% purity of the crude product.

[f] Yield calculated from ^{1}H-N.M.R. spectrum; the recrystallized product was isolated in 32% yield.

4-(2-Hydroxy-2-propyl)-2-phenyl-4,5-dihydro-1,3-thiazole-4-carboxylic Acid (5e):

A solution of butyllithium (4.1 mmol) in *n*-hexane is slowly added to a magnetically stirred solution of 2-phenyl-4,5-dihydro-1,3-thiazole-4-carboxylic acid (**3a**; 0.415 g, 2 mmol) in tetrahydrofuran (35 ml) under nitrogen at −78°. Stirring is continued at −78° for 1 h. Then, acetone (0.3 ml, 4 mmol) is added whereupon the deep red, clear solution decolorizes. After 3 h, the cold (−78°) solution is poured into saturated aqueous sodium chloride solution (30 ml) containing conc. hydrochloric acid (10 mmol). The mixture is extracted with ether, the extract dried and evaporated, and the residue recrystallized from chloroform/ether; yield: 0.45 g (85%); m.p. 158–160° (dec).

$C_{13}H_{15}NO_3S$	calc.	C 58.89	H 5.70	N 5.28
(265.3)	found	58.60	5.85	5.48

I.R. (KBr): $\nu_{max} = 3160$ (OH, broad); 1615 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.1–7.35$ (m, $5H_{arom}$); 4.23 (s, 2H, OH); 3.9 (s, 2H, H-5); 1.4 (s, 3H, CH_3); 1.32 ppm (s, 3H, CH_3).

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