Reaction of 3-Hydroxyisoindolin-1-ones with Lawesson Reagent. Synthesis of Isoindoline-1-thiones

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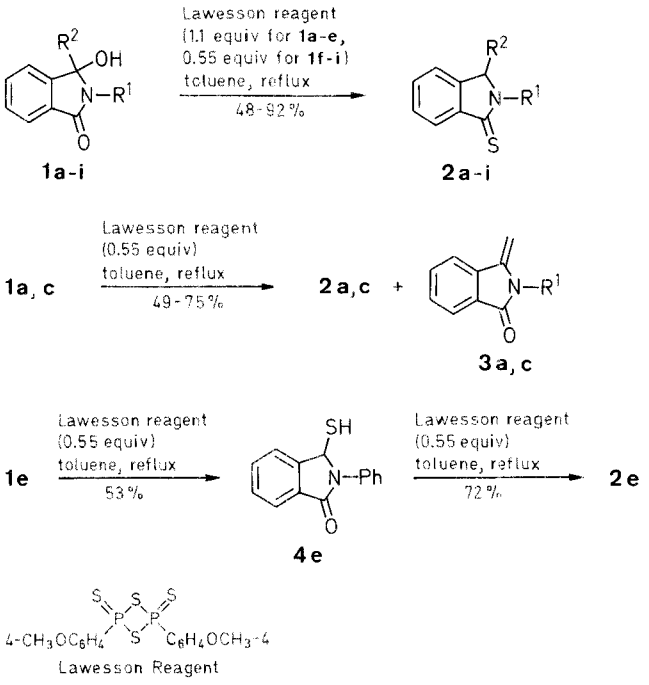
Treatment of 3-hydroxyisoindolin-1-ones **1** with Lawesson reagent gave isoindoline-1-thiones **2**, by direct thionation and reductive elimination of hydroxy group, in good yields.

2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson reagent) is known to be an excellent reagent for the thionation of carbonyl to thiocarbonyl compounds.[1] In the course of our studies on the reactivity of cyclic thioamide systems,[2] we found that 3-hydroxyisoindolin-1-ones **1** react with Lawesson reagent to yield isoindoline-1-thiones **2** in good yields by the direct thionation of the amide carbonyl and reductive elimination of the hydroxy group. Herein we describe the results of our studies of this novel reaction.

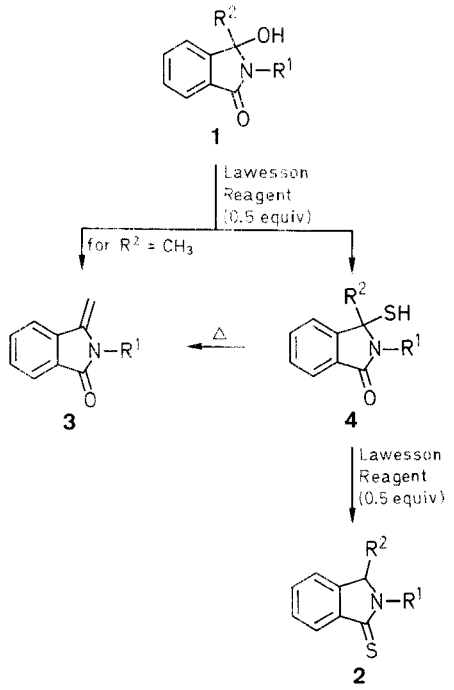
When 3-hydroxyisoindolin-1-ones **1a** and **1c** were heated to reflux with 0.55 molar equivalent of Lawesson reagent in toluene under an argon atmosphere, isoindoline-1-thiones **2a** and **2c**, and the dehydration products, 3-methylideneisoindolin-1-ones **3a** and **3c**, were obtained. On the other hand, isoindoline-1-thiones **2a–e** were exclusively produced when 3-hydroxyisoindolin-1-ones **1a–e** were treated with 1.1 molar equivalent of Lawesson reagent under the same conditions (Scheme A) (Tables 1 and 2).



Scheme A

The structure of the products **2a–e**, **3a**, and **3c** were confirmed on the basis of their spectral properties and elemental analyses. When 3-hydroxy-2-phenylisoindolin-1-one (**1e**) was refluxed with 0.55 molar equivalent of Lawesson reagent, a different product was formed. From its spectral [IR, ν = 2550 cm^{-1}(SH)] and analytical data (Table 2), it was characterized as 3-mercapto-2-phenylisoindolin-1-one (**4e**). Mercapto derivative **4e** thus obtained was heated with Lawesson reagent in toluene under reflux to give the isoindoline-1-thione **2e** in 72% yield, while in the absence of Lawesson reagent **4e** was recovered quantitatively. Treatment of 3-hydroxyisoindolin-1-ones **1f–i**, which have an aryl substituent at 3-position, with 0.55 molar equivalent of Lawesson reagent gave isoindoline-1-thiones **2f–i** in 48–88% yield by the direct thionation of the amide carbonyl and reductive elimination of the hydroxy group. Although the mechanism for the formation of the products **2**, **3**, and **4** is not clear at present, we postulate the reaction path as shown in the Scheme **B**.

The reactions described here suggest a mode of action of Lawesson reagent as dehydration as well as thionation reagent.



Scheme **B**

Table 1. Reaction of **1** with Lawesson Reagent

Isoindolin-1-one	R^1	R^2	Molar Ratio LR[a]/1	Reaction Time (min)	Products, Yield (%)[b] 2	3	4
1a	Ph	CH_3	0.55	60	15	49	–
			1.1	15	68	trace	–
1b	4-$CH_3C_6H_4$	CH_3	1.1	15	71	–	–
1c	4-ClC_6H_4	CH_3	0.55	60	trace	75	–
			1.1	15	92	trace	–
1d	*n*-Pr	CH_3	1.1	10	82	–	–
1e	Ph	H	0.55	10	11	–	53
			1.1	10	64	–	–
1f	Ph	Ph	0.55	10	88	–	–
1g	$PhCH_2$	Ph	0.55	10	48	–	–
1h	*n*-Pr	Ph	0.55	10	70	–	–
1i	CH_3	Ph	0.55	5	65	–	–

[a] LR = Lawesson reagent.
[b] Yield of isolated products **2**–**4**.

3-Hydroxyisoindolin-1-ones **1a–f** and **1i** were prepared as described in the literature[3–5] and **1g** and **1h** were prepared by a modification of this method.

3-Hydroxy-3-phenyl-2-benzylisoindolin-1-one (**1g**); yield: quant.; mp 145–147 °C.

$C_{21}H_{17}NO_2$ (315.4) calc. C 79.98 H 5.43 N 4.44; found 79.69 5.39 4.34

IR (KBr): ν = 3260, 1660 cm^{-1}.

Table 2. Isoindoline-1-thiones **2**, Isoindolin-1-ones **3**, and 3-Mercaptoisoindolin-1-one **4e** Prepared

Product	mp (°C)[a]	Molecular Formula[b] or Lit. mp (°C)	IR (KBr)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ
2a	109–111	$C_{15}H_{13}NS$ (239.3)	1465, 1315, 1290	1.40 (d, 3H, J = 6.8); 5.22 (q, 1H, J = 6.8); 7.15–7.70 (m, 8H); 8.03–8.19 (m, 1H)	18.2 (q); 66.2 (d); 121.2 (d); 126.0 (d); 127.1 (d); 128.0 (d); 128.6 (d); 129.2 (d); 131.8 (d); 138.3 (s); 138.5 (s); 144.6 (s); 193.2 (s)
2b	104–106	$C_{16}H_{15}NS$ (253.4)	1470, 1320, 1290	1.40 (d, 3H, J = 6.8); 2.40 (s, 3H); 5.16 (q, 1H, J = 6.8); 7.11–7.98 (m, 7H); 8.03–8.19 (m, 1H)	18.3 (q); 21.2 (q); 66.3 (d); 112.9 (d); 126.0 (d); 127.0 (d); 128.6 (d); 130.0 (d); 131.8 (d); 135.7 (s); 138.1 (s); 138.9 (s); 144.7 (s); 193.3 (s)
2c	115.5–117	$C_{15}H_{12}ClNS$ (273.8)	1485, 1325, 1285	1.41 (d, 3H, J = 6.8); 5.21 (q, 1H, J = 6.8); 7.35–7.71 (m, 7H); 8.07–8.17 (m, 1H)	18.1 (q); 66.1 (d); 121.2 (d); 126.0 (d); 128.4 (d); 128.7 (d); 129.4 (d); 132.0 (d); 133.6 (s); 136.7 (s); 138.6 (s); 144.4 (s); 193.5 (s)
2d	73–74	$C_{12}H_{15}NS$ (205.3)	1475, 1455, 1295	1.67 (t, 3H, J = 7.3); 1.54 (d, 3H, J = 6.8); 1.63–2.01 (m, 2H); 3.40–3.69 (m, 1H); 4.31–4.62 (m, 1H); 4.77 (q, 1H, J = 6.8); 7.26–7.64 (m, 3H); 7.92–8.10 (m, 1H)	11.3 (q); 17.5 (q); 20.8 (t); 46.1 (t); 63.1 (d); 121.1 (d); 125.4 (d); 128.2 (d); 131.2 (d); 138.6 (s); 144.8 (s); 192.9 (s)
2e	167–168.5	168[6]	1470, 1435, 1325, 1295	5.01 (s, 2H); 7.24–7.71 (m, 8H); 8.07–8.18 (m, 1H)	68.2 (t); 121.7 (d); 125.5 (d); 126.2 (d); 127.6 (d); 128.5 (d); 129.1 (d); 131.7 (d); 139.0 (s); 139.9 (s); 140.3 (s); 193.7 (s)
2f	139–140	$C_{20}H_{15}NS$ (301.4)	1460, 1315, 1295	6.10 (s, 1H); 6.93–7.40 (m, 11H); 7.42–7.62 (m, 2H); 8.11–8.29 (m, 1H)	75.0 (d); 122.5 (d); 126.0 (d); 127.2 (d); 127.8 (d); 127.9 (d); 128.9 (d); 132.2 (d); 135.7 (s); 138.6 (s); 138.9 (s); 144.3 (s); 194.4 (s)
2g	146–148	$C_{21}H_{17}NS$ (315.4)	1440, 1305	3.97 (d, 1H, J = 14.7); 5.46 (s, 1H); 6.19 (d, 1H, J = 14.7); 6.96–7.56 (m, 13H); 8.12–8.22 (m, 1H)	47.8 (t); 70.7 (d); 122.3 (d); 126.0 (d); 127.8 (d); 128.5 (d); 128.6 (d); 129.0 (d); 129.2 (d); 131.8 (d); 135.4 (s); 136.2 (s); 138.4 (s); 144.8 (s); 193.5 (s)
2h	97–98	$C_{17}H_{17}NS$ (267.4)	1470, 1310	0.90 (t, 3H, J = 7.3); 1.50–1.89 (m, 2H); 3.01–3.30 (m, 1H); 4.29–4.59 (m, 1H); 5.66 (s, 1H); 7.00–7.58 (m, 8H); 8.02–8.20 (m, 1H)	11.4 (q); 20.8 (t); 46.5 (t); 71.9 (d); 122.2 (d); 125.5 (d); 127.6 (d); 128.5 (d); 129.0 (d); 129.2 (d); 131.6 (d); 135.5 (s); 138.7 (s); 144.6 (s); 193.1 (s)
2i	139–140	$C_{15}H_{13}NS$ (239.3)	1445, 1315	3.31 (s, 3H); 5.56 (s, 1H); 7.03–7.20 (m, 3H); 7.23–7.54 (m, 5H); 8.03–8.17 (m, 1H)	32.6 (q); 73.7 (d); 122.2 (d); 125.3 (d); 127.4 (d); 128.5 (d); 129.0 (d); 129.2 (d); 131.6 (d); 135.4 (s); 138.5 (s); 144.5 (s); 193.2 (s)
3a	97–98	97–98[7] 99–100[8]	1705, 1640	4.90 (d, 1H, J = 2.0); 5.21 (d, 1H, J = 2.0); 7.24–7.96 (m, 9H)	90.4 (t); 120.0 (d); 123.5 (d); 128.1 (d); 128.9 (s); 129.3 (d); 129.7 (d); 132.3 (d); 134.6 (s); 136.3 (s); 143.1 (s); 166.6 (s)
3c	115–116	$C_{15}H_{10}ClNO$ (255.7)	1700, 1635	4.80 (d, 1H, J = 2.0); 5.24 (d, 1H, J = 2.0); 7.26–8.00 (m, 8H)	90.3 (t); 120.1 (d); 123.6 (d); 129.3 (d); 129.5 (d); 129.8 (d); 132.4 (d); 133.0 (s); 133.7 (s); 134.4 (s); 136.1 (s); 142.8 (s); 166.4 (s)
4e	112–113	$C_{14}H_{11}NOS$ (241.3)	2550, 1685	2.37 (d, 1H, J = 7.6); 6.23 (d, 1H, J = 7.6); 7.17–7.68 (m, 8H); 7.80–7.93 (m, 1H)	58.0 (d); 122.1 (d); 122.5 (d); 122.7 (d); 124.7 (d); 127.8 (d); 128.1 (d); 129.7 (s); 131.3 (d); 134.9 (s); 142.8 (s); 164.5 (s)

[a] Uncorrected, measured with a Yanaco micro melting point apparatus.

[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.06, N ±0.07.

[c] Recorded on a Hitachi 260-30 IR spectrophotometer.

[d] Obtained on a JEOL FX 100 spectrometer at 100 MHz.

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.05 (d, 1H, J = 14.8 Hz); 4.05 (s, 1H); 4.51 (d, 1H, J = 14.8 Hz); 7.13–7.50 (m, 8H); 7.22 (s, 5H); 7.61–7.71 (m, 1H).

^{13}C-NMR ($CDCl_3$): δ = 42.9 (t); 91.5 (s); 122.7 (d); 123.3 (d); 126.3 (d); 126.8 (d); 128.0 (d); 128.2 (d); 128.7 (d); 129.3 (d); 130.1 (s); 132.6 (d); 137.8 (s); 138.3 (s); 149.1 (s); 168.0 (s).

3-Hydroxy-3-phenyl-2-propylisoindolin-1-one (**1h**); yield: 67%; mp 184–185°C.

$C_{17}H_{17}NO_2$ (267.3)	calc.	C 76.38	H 6.41	N 5.24
	found	76.01	6.40	5.27

IR (KBr): ν = 3150; 1670 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.73 (t, 3H, J = 6.8 Hz); 1.10–1.60 (m, 2H); 2.70–3.00 (m, 1H); 3.16–3.46 (m, 1H); 4.23 (s, 1H); 7.21–7.64 (m, 9H).

^{13}C-NMR ($CDCl_3$): δ = 11.7 (q); 21.9 (t); 41.3 (t); 91.4 (s); 122.7 (d); 123.1 (d); 126.2 (d); 128.4 (d); 129.3 (d); 130.6 (s); 132.5 (d); 138.9 (s); 149.1 (s); 167.9 (s).

Thionation of 3-Hydroxyisoindolin-1-ones 1; General Procedure:
A solution of 3-hydroxyisoindolin-1-one **1** (10 mmol) and Lawesson reagent (5.5 mmol or 11 mmol) in toluene (50 mL) is refluxed under an argon atmosphere for 5–60 min. After removal of the solvent under reduced pressure, the residue is chromatographed on a silica gel (Wakogel C-300 or Merck Kieselgel 60, flash chromatography) column with benzene/*n*-hexane (1:1 to 9:1) as eluent to afford **2** and/or **3** or **4** (Tables 1 and 2).

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