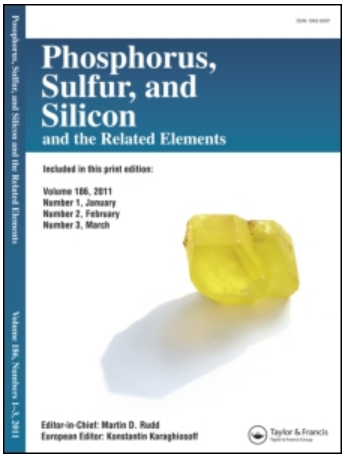

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ON THE REACTION OF BENZOHYDROXAMIC ACIDS WITH LAWESSON'S REAGENT

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ON THE REACTION OF BENZOHYDROXAMIC ACIDS WITH LAWESSON'S REAGENT

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Reaction of Lawesson's Reagent (LR) with two N-alkyl benzohydroxamic acids is presented. In addition to the desired thiohydroxamic acids **2,** the reduction process provides amides **3** and thioamides **4.** An unexpectedly pronounced solvent effect on the course of the reaction was observed. The best yields (40–50%) of **2a** were obtained in THF, and in this solvent amide **3a** was not formed. In HMPA solution the amide **3a** and the thioamide **4a** were the only products, and **2a** was not formed at all.

Keywords: Hydroxamic acids; Lawesson's Reagent; thiohydroxamic acids; thioamides

INTRODUCTION

Thiohydroxamic acids are interesting as potential novel complexing and biologically active agents. They are usually prepared by three-step procedures involving N-hydroxy group protection and deprotection, the methods are laborious and generally give low yield of products, typically 10 - 50 %.[3] Therefore, we decided to investigate preparation of thiohydroxamic acids[1] directly from parent hydroxamic acids, as this would open a promising, direct route to thiohydroxamic acids, starting from naturally occurring hydroxamate siderophores[2] and other hydroxamate ligands.

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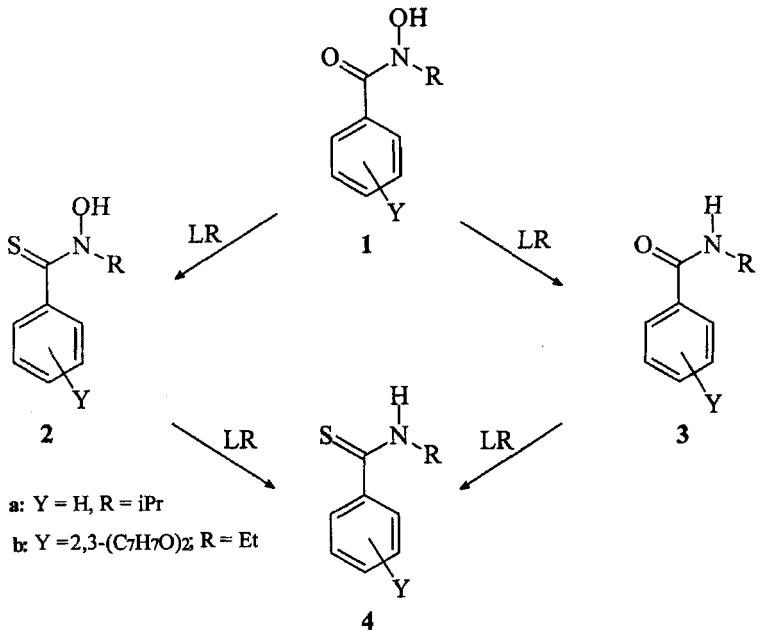
RESULTS AND DISCUSSION

Our initial experiments with Lawesson's reagent (LR) – the most popular thionation agent[4] – showed that it smoothly reacts with N-alkyl benzohydroxamic acids **1a** and **1b** to yield the desired thiohydroxamic acids **2,** and unexpectedly, amides **3** and thioamides **4.**



SCHEME

It seems that first steps of the reaction involve conversion of hydroxamic acids **1** to the thiohydroxamic acids **2** *via* typical O/S-exchange mechanism, and a parallel reduction of **1** to the amide **3.** Next, both **2** and **3** are transformed simultaneously to the thioamides **4.** In a control experiment the isolated thiohydroxamic acid **2a** was reacted with LR in benzene for 16 hrs at rt., to afford the thioamide **4a** in 38% yield. Under the same conditions amide **3a** gave **4a** in 79% yield. These results supported the above mentioned hypothesis, and additionally showed that thionation of the amide **3a** in benzene is about 2-times faster than reduction of the corresponding thiohydroxamic acid **2a.**

The products ratios in reaction mixtures were determined by ^{1}H NMR, by comparison of intensities of the N-alkyl protons signals. For transformations of **1a** both the α-methine and methyl protons were of diagnostic value, while in case of **1b** only methyl protons could be taken into account, due to overlapping of two quartets of methylene protons (two rotamers) from **1b**, with corresponding signals of **2b, 4b,** and the CH_3 signals of anisylphosphine trioxide always formed from LR. The results are presented in Table.

TABLE Reactions of Lawesson's Reagent (LR) with benzohydroxamic acids **1**

Entry #	*HA*	*LR [equiv]*	*Solvent*	*Temp. /time [°C/h]*	*Reaction mixture [%]**			
					1	*2*	*3*	*4*
1	**1a**	0.5	$CHCl_3$	60/3	17	35	34	14
2	**1a**	1.0	$CHCl_3$	60/3	5	27	23	45
3	**1a**	0.5	HMPA	80/3	5	-	56	39
4	**1a**	1.0	HMPA	80/3	6	-	42	52
5	**1a**	0.5	Benzene	80/3	28	26	36	10
6	**1a**	1.0	Benzene	80/2	-	-	3	97
7	**1a**	0.5	THF	25/16	24	55	-	21
8	**1a**	0.5	THF	-70/6+25/16	14	63	-	23
9	**1a**	0.5	THF	65/2**	10	57	16	17
10	**1a**	1.0	THF	25/16	12	39	-	49
11	**1b**	0.5	$CHCl_3$	60/3	9	12	57	22
12	**1b**	1.0	$CHCl_3$	60/3	11	10	31	48
13	**1b**	2.0	$CHCl_3$	25/48	54	10	18	18
14	**1b**	1.0	Benzene	80/3	12	12	15	61
15	**1b**	0.5	THF	25/2	28	36	20	17
16	**1b**	0.5	THF	25/48	18	34	9	38

* As determined by ^{1}H NMR spectroscopy; percentage calculated on the basis of the total amount of **1**.
**LR solution was added dropwise during 2 h.

In ethanol-free chloroform all listed above products are obtained, and **1a** gives better yields of the corresponding thiohydroxamic acid **2a** than **1b** (entries 1,2 and 11–13).

0.5 Equiv. of LR in benzene leads to 72% consumption of **1a** with domination of the amide **3a** in the reaction mixture, and **2a** is formed in only 19% yield (entry 5). An excess of LR yields almost quantitatively the thioamide **4a** (entry 6).

In HMPA solution, the desired thiohydroxamic acid **2a** is not detected in reaction mixtures at all. In that case, an excess of LR gives only a small increase of the **4a:3a** ratio (entries 4 and 5). Reaction in THF solution can be performed at room temperature, and the yield of thiohydroxamic acid **2a** is the highest (40–50%). The reaction mixtures contain only **2a, 4a,** and unreacted **1a** (entries 7–10). This indicates that in this solvent, at rt. reduction of **1a** to the amide **3a** does not take place. Therefore, **4a** can only be formed directly from **2a.** Performing the reaction at low temperature gives better yield of the desired **2a** (entry 8).

In boiling THF **3a** is formed to some extent even during a slow addition of LR solution (entry 9). For reactions of **1b** in THF solution, the yields of the thiohydroxamic acid **2b** are lower (about 30%) and in each case formation of the amide **3b** is observed (entries 15, 16).

An attempted aqueous workup of reaction mixtures from bulk **1b** completely failed probably due to high lipophilicity of sodium salts of **1b** and **2b.** These products could be separated only by column chromatography.

EXPERIMENTAL

NMR spectra were recorded on Varian spectrometers operating at 200 and 500 MHz (^{1}H) in $CDCl_3$ solutions. Mass spectra were measured with an AMD 604 apparatus. THF was distilled over potassium/benzophenone, benzene over sodium, and HMPA was distilled at reduced pressure. Lawesson's reagent (Fluka) was washed with chloroform, diethyl ether and dried prior to use. TLC analysis was performed with eluent system A (2:1, chloroform – hexane) and B (5:1, benzene – EtOAc). All reactions were carried out under argon atmosphere.

N-benzoyl-N-isopropylhydroxylamine **1a** was prepared by benzoylation of N-isopropylhydroxylamine [5], mp 101°C. TLC R_f 0.10 (A); ^{1}H NMR

1.30 (d, 6H), 4.20 (sp, 1H), 6.70 (br. s, OH, 1H), 7.40–7.58 (m, 5H); ^{13}C NMR 20.0, 52.1, 127.5 (C-2/6), 128.3 (C-3/5), 130.8 (C-4), 133.0 (C-1), 166.4 (C=O)

N-(2,3-dibenzyloxybenzoyl)-N-ethylhydroxylamine **1b** was obtained as described in the literature.[6] TLC R_f 0.07 (A);^1H NMR 1.20 (2 × t, 3H), 3.48 and 3.75 (2 × q, 2H, intensities 2:1), 5.05 and 5.15 (2 × s, 4H), 7.0–7.4 (m, 13H); ^{13}C NMR 11.9, 12.3, 43.0, 44.2, 71.0, 71.5, 116.0, 118.4, 120.2, 122.0, 125 (four signals), 127.5–129.0 (group of signals), 136.0, 152.0, 162.0 (C=O)

N-isopropylbenzamide **3a** was obtained as described in the literature [7], mp 98–101°C. TLC R_f 0.62 (A); ^1H NMR 1.26 (2 × d, 6H), 4.29 (2 × sp, 1H), 6.0 (br. s, NH, 1H), 7.42 (t, 2H), 7.48 (t, 1H), 7.75 (d, 2H); ^{13}C NMR 22.8, 41.8, 126.8 (C-2/6), 128.4 (C-3/5), 131.2 (C-4), 134.9(C-1), 166.3 (C=O)

N-ethyl-2,3-dibenzyloxybenzamide **3b** was obtained from 2,3-dibenzyloxybenzoic acid N-hydroxysuccinimide ester and aqueous N-ethylamine solution in 70% yield. A yellow oil. TLC R_f 0.19 (A); ^1H NMR 1.01 (t, 3H), 3.32 and 3.36 (2 × q, 2H), 5.09 and 5.17 (2 × s, 4H), 7.16 (m, 2H), 7.35–7.55 (m, 10H), 7.78 (m, 1H), 8.90 (br s, NH); ^{13}C NMR 14.3, 34.4, 71.2, 76.3, 116.7, 123.2, 124.4, 127.6, 128.5 (five signals), 136.3, 136.4, 146.7, 151.6, 164.8 (C=O)

Reaction of 1a with LR (entry 8)

LR (101 mg, 0.25 mmol) was added to a solution of **1a** (90 mg, 0.5 mmol) in THF (5 ml), the mixture was stirred for 16 hr at rt, and the solvent was evaporated. The residue was dissolved in methylene chloride (5 ml) and extracted with 1 M NaOH solution (3 × 2 ml). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification on silica gel column in chloroform gave 16 mg (18%) of the thioamide **4a.** The combined aqueous alkaline extracts were cooled in ice and carefully acidified with 6 M HCl to pH 3. The resulting milky suspension was reextracted with CH_2Cl_2 and after drying the products were separated on silica gel column in chloroform to give 44 mg (45%) of **2a** as the first fraction, and 12 mg (13%) of the starting hydroxamic acid **1a.**

Reaction of 1b with LR (entry 15)

LR (142 mg, 0.35 mmol) was added to a solution of **1b** (264 mg, 0.7 mmol) in THF (6 ml), the mixture was stirred 2 hr at rt, and the solvent was evaporated. The residue was dissolved in methylene chloride (10 ml), washed with water (3 × 2 ml), dried over $MgSO_4$, and concentrated under vacuum. Repeated on silica gel column using benzene - methanol (10:1) system yielded 44 mg (16%) of **2b** as the first fraction and 30 mg (11%) of the thioamide **4b**.

The spectral data of these compounds are as follows:

2a: yellow oil; TLC R_f 0.58 (A); ^{1}H NMR 1.37 (d, 6H), 4.44 (sp, 1H), 7.36–7.44 (m, 5H), 8.70 (br. s, OH); ^{13}C NMR 19.23 (74%, CH_3), 54.78 (25%, CH), 125.74 (66%, C-2/6), 128.04 (81%, C-3/5), 128.95 (39%, C-4), 137.61 (8%, C-1), 179.83 (9%, C=S); MS-EI [m/e] 195 (6%) M^+, 179 (16%) $[M-16]^+$, 178 (42%) $[M-OH]^+$, 146 (8%) $[M-SOH]^+$, 121 (100%) $[C_6H_5CS]^+$, 105 (20%), 77 (32%), HRMS: 195.07078 (calcd for $C_{10}H_{13}NOS$ 195.07179).

2b: colourless oil, TLC R_f 0.57 (A); ^{1}H NMR 1.23 (t, 3H), 3.73 (2 × q, 2H), 4.98, 5.24 (2 × d, J = 10 Hz, 2H), 5.17 (s, 2H), 6.93 (t, 1H), 7.19 (d, 2H), 7.30–7.50 (m, 10H); ^{1}H NMR (benzene-d_6) 0.79 (t, 3H), 3.30 (2 × q, 2H), 4.58, 4.62 (2 × d, J = 10 Hz, 2H), 5.06, 5.15 (2 × d, J = 10 Hz, 2H), 6.54 (dd, J = 7.8 Hz, J = 1 Hz, 1H), 6.70 (t, J = 7.8 Hz, 1H), 6.95 (dd, J = 7.8 Hz, J = 1 Hz, 1H), 7.0–7.2 (m, 9H), 7.40 (dd, J = 7.8 Hz, J = 1 Hz, 1H), 11.55 (s, 1H, OH); ^{13}C NMR (benzene-d_6) 12.28, 48.00, 70.90, 75.68, 115.0, 121.42, 124.67, 127.5–129.1 (group of signals), 134.34, 136.89, 137.75, 143.65, 152.52, 177.05 (C=S), MS-EI [m/e] 393 (0.7%) M^+, 377 (0.9%) $[M-16]^+$, 376 (2.7%) $[M-OH]^+$, 344 (76%) $[M-SOH]^+$, 333 (7.7%) $[ArCS]^+$, 91 (100%), HRMS: 393.14115 (calcd for $C_{23}H_{23}NO_3S$ 393.13987).

4a: yellow oil; TLC R_f 0.32 (A); ^{1}H NMR 1.28 (d, 6H), 4.81(sp, 1H), 7.36–7.42 (br.s, 1H, OH), 7.38 (t, 2H, H-meta), 7.42 (t, 1H, H-para), 7.70 (dd, 2H, H-orto); ^{13}C NMR 21.4 (CH_3), 48.0 (CH), 126.5, 128.4, 130.8 (C-4), 142.3 (C-1), 197.8 (C=S); MS-EI [m/e] 179 (100%) M^+, 163 (5%) $[M-1-CH_3]^+$, 146 (8%) $[M-SH]^+$, 136 (5%) $[C_6H_5C(S)NH]^+$, 121(70%) $[C_6H_5CS]^+$

4b: white needles, mp. 77°C (EtOAc-hexane) TLC R_f 0.37 (A); ^{1}H NMR 1.09 (t, 3H), 3.70 (2 × q, 2H), 5.0 + 5.17 (2 × s, 4H), 7.1 (2 × t, 2H), 7.25–7.50 (m, 10H), 7.88 (dd, 1H-orto), 9.0 (br.s, 1H, OH); ^{13}C NMR

12.6, 41.7, 71.1, 71.2, 76.3, 77.0, 115.8, 124.2, 125.2, 127.6–128.8 (group of signals), 133.8, 136.3, 144.0, 152.0, 194.7 (C=S); MS-EI [m/e] 377 (1%) M^+, 344 (65%) $[M\text{-}SH]^+$, 286 (10%) $[M\text{-}91]^+$, 254(5%) $[M\text{-}SH\text{-}91]^+$

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References

[1] W. Walter and E. Schaumann, *Synthesis,* 111 (1971).
[2] M. J. Miller, *Chem. Rev.* **89,** 1563 (1989).
[3] a) D. St. Black et al., *Aust. J. Chem.* **41,** 47 (1988),
b) S. Rzepa et al, *Synthesis,* 829 (1984).
[4] M. P. Cava and M. I. Levinson, *Tetrahedron,* **41,** 5061 (1985).
[5] W. Kliegel and D. Nanninga, *Chem. Ber.,* **116,** 2616 (1983).
[6] L. Nakonieczna and A. Chimiak, *Synthesis,* 418 (1987).
[7] J. H. Brown and C. H. Bushweller, *J. Am. Chem. Soc.,* **117,** 12567 (1995).