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Lawesson's Reagent for Direct Thionation of Hydroxamic Acids: Substituent Effects on LR Reactivity

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ABSTRACT: *To explore the generality and scope of direct thionation of hydroxamic acids (HAs), the reaction of various structurally diverse HAs with Lawesson's reagent was investigated. The yield of thiohydroxamic acid (THAs) is poor when HAs possess bulky acyl and/or N-substituents, acidic α-hydrogen atoms, or an N-phenyl ring. THAs yields were correlated with Brown sigma parameter. The relative rates of two subsequent processes k_{T_2} and k_{R_2} were also measured. Correlation was also found for methine proton chemical shifts of N-isopropyl benzothiohydroxamic acids.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:676–684, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20259

INTRODUCTION

N-Substituted thiohydroxamic acids (THAs) **2** can be obtained using two different methods [1]: (i) thioacylation of the respective hydroxylamines or (ii) thionation of hydroxamic acids (HAs) **1**. The scope of the first approach is often limited by availability of a stable thioacylating agent. Recently, a highly efficient class of *S*-thioacyldithiophosphates has been successfully introduced [2]. With few exceptions (thiopivaloyl-, phenylthioacetyl-, and arothioyl-containing electron-donating groups), *S*-thioacyldithiophosphates produce THAs in moderate to very good yields.

On the other hand, direct thionation of HAs is of great interest since this route provides a synthetic pathway to thioanalogues of natural hydroxamate siderophores. Also the synthesis of *N*-hydroxythiopeptides has recently begun to attract considerable attention [3]. Unfortunately, thionation with P_4S_{10} produces complex mixtures containing only small quantities of the desired THAs [4,5]. Rzepa and coworkers [6] proposed an approach that involved a three-step procedure with protection and deprotection of the N—OH moiety during the synthesis of THAs using Lawesson's reagent (LR), but yields of the corresponding THAs **2** were low (10–50%), probably because of lability of *O*-acetylthiohydroxamic acids.

Previously [7], we managed to optimize certain parameters for obtaining THAs **2B** directly from their parent benzohydroxamic acids **1B** using LR. We showed that the reaction of benzohydroxamic acids with LR should be performed in THF at room temperature, using 0.5 equivalent of LR. This procedure allows for obtaining the desired *N*-alkyl benzothiohydroxamic acids in moderate yields (40–60%). In addition, we found that this reaction generates also the corresponding benzamides **3B** and thiobenzamides **4B** as by-products. Furthermore, we proved the coexistence of four independent processes: two parallel—the benzohydroxamic acid thionation (T_1) and deoxygenation (R_1)

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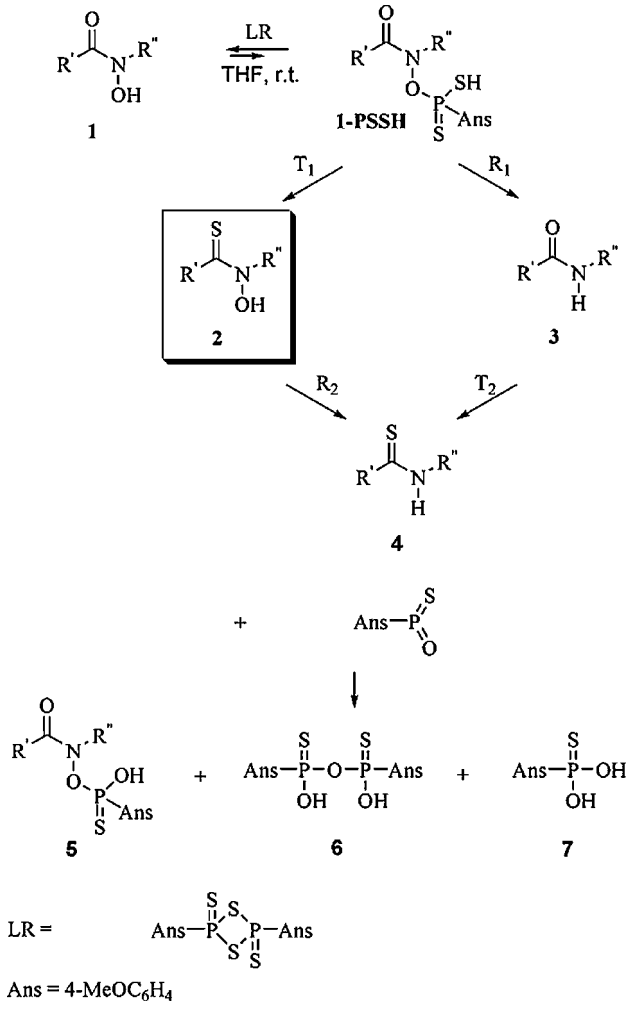
pathways—and two subsequent steps involving reduction of benzothiohydroxamic acid **2B** (R_2) and thionation of benzamide **3B** (T_2). Also the mechanism of LR action on HAs **1** was proposed [8]. According to the suggested mechanism, anisyldithiophosphorane (AnsPSS) generated from LR attacks the hydroxyl group of HA **1** yielding an elusive adduct, the *O*-dithiophosphonylated HA **1-PSSH**. Its stability depends on the N—O bond energy. Breakdown of **1-PSSH** gives amides **3**. As formation of adduct **1-PSSH** is a reversible process, a further reaction on the carbonyl oxygen atom of AnsPSS occurs, which leads to THA **2** and anisylthiophosphorane (AnsPOS). Next AnsPOS, generated by thionation and deoxygenation of HA **1**, is transformed into *O*-thiophosphonylohydroxamic acid **5** and finally into pyrothiophosphonate **6** in the presence of anisylthiophosphonic acid **7** (Scheme 1).



SCHEME 1

Significant acidity of THAs **2** facilitates their isolation and purification from reaction mixtures. Because anisylthiophosphonic acid **7** is the main phosphorus-containing product formed from LR in the course of thionation of HAs **1**, basic aqueous workup affords a mixture of THA **2** and anisylthiophosphonic acid **7** salts. After acidification, this mixture can be easily separated on short silica gel columns owing to marked difference of polarities of both components.

Until now, reported studies regarding the electronic effect of substituents on the thionation rate of carbonyl compounds have been limited to carboxylic esters only. Bradshaw showed that esters with electron-withdrawing groups treated with LR do not give the corresponding thionoesters in isolable yields while conjugated electron-donating groups increased the rate of their thionation [9]. He also found that *tert*-butyl benzoate failed to react with LR due chiefly to steric hindrance. Amides are better nucleophiles and therefore react with LR much faster than esters, but the effect of substituents on the thionation rate of amides has never been studied [10]. In the previous report [8], it was found that EWG-substituted HAs give better yields of the corresponding THAs **2**. It can be assumed that this effect results from both lower nucleophilicity and stronger N—O bond of EWG-substituted HAs as compared with EDG-substituted ones. This is quite opposite to the above-mentioned tendency observed by Bradshaw for carboxylates. In addition, it was observed that the reaction of HAs **1** with LR is even faster than that of amides.

RESULTS AND DISCUSSION

To determine the scope, limitations, and substituent effects of direct thionation of HAs with LR, more than 30 selected *N*-substituted HAs **1** were subjected to LR action in THF at room temperature.

Examples include aliphatic and aromatic HAs, **1A** and **1B**, respectively, with steric extremes of acyl ($R' = Me$, *t*-Bu, mesityl) and *N*-substitution ($R'' = Me$, *t*-Bu); *N*-aryl HAs **1Ad–f** ($R'' = aryl$); cinnamohydroxamic acid **1An** and *N*-isopropyl benzohydroxamic acids **1Bf–s** including substituents with varying electronic effect in their aromatic rings (Table 1). The reaction was monitored by TLC using the Fe^{3+} test. Upon treatment with methanolic solution of ferric chloride, HAs and THAs give magenta and black stain, respectively. Quantitative analyses were performed using ^1H NMR by means of following the appearance of the methyl, methylene, or methine proton signals of THA **2** and other products of HA transformations. The yield of THA **2** formed was

TABLE 1 Results of Direct Thionation of Hydroxamic Acids R′CON(OH)R″ **1** Using LR

Entry	*HA*	*R′*	*R″*	*THA* **2** *(%)*[a]	*THA* **2** *Diagnostic Protons (δ ppm)*	*Other Products (%)*[a]			
						1	**5**	**3**	**4**
1	**1Aa**	Me	Bn	46	2.62; 5.09	10	15	0	31
2	**1Ab**	Me	*i*Pr	30	2.57; 4.55	**1** + **5** + **3** 38			38
3	**1Ac**	Me	*t*-Bu	15	1.63; 2.76	21	[b]	20	29
4	**1Ad**	Me	Ph	<5	2.50; 11.3	13	[b]	50	28
5	**1Ae**	Me	4-$NO_2C_6H_4$	nd	–	24	[b]	11	44
6	**1Af**	Me	4-$MeOC_4H_4$	nd	–	22	[b]	56	10
7	**1Ag**	*n*-Pr	Me	35	2.67; 3.60	20	16	4	20
8	**1Ah**	*n*-Pr	*i*Pr	44	2.74; 4.58	11	13	13	10
9	**1Ai**	*n*-Pr	*t*-Bu	nd	–	12	12	41	35
10	**1Aj**	*t*-Bu	Me	nd	–	nd	nd	41	23
11	**1Ak**	*t*-Bu	*i*Pr	nd	–	100	–	–	–
12	**1Al**	Bn	Me	nd	–	10	nd	nd	54
13	**1Am**	EtO_2CCH_2	Me	nd	–			[b]	
14	**1An**	PhCH=CH	*i*Pr	<5	4.50	**1** + **5** 43		6	45
15	**1Ba**	Ph	Me	25	3.57	17	14	17	26
16	**1Bb**	Ph	Bn	29	5.02	24	15	7	24
17	**1Bc**	Ph	*t*-Bu	nd	–	3	–	92	5
18	**1Bd**	Ph	Ph	nd	–	[b]	[b]	54	36
19	**1Be**	2,4,6-$(CH_3)_3C_6H_2$	Me	nd	–	10	25	58	–
20	**1Bf**	4-$Me_2NC_6H_4$	*i*Pr	nd	–	8	14	48	30
21	**1Bg**	4-$BnOC_6H_4$	*i*Pr	14	4.53	13	5	41	21
22	**1Bh**	4-$MeOC_6H_4$	*i*Pr	16 (10[c])	4.52	13	11	41	11
23	**1Bi**	4-*t*-BuC_6H_4	*i*Pr	24 (15[c])	4.51	**1** + **5** + **3** 43			33
24	**1Bj**	4-MeC_6H_4	*i*Pr	25	4.48	15	11	18	26
25	**1Bk**	Ph	*i*Pr	38	4.44	11	14	7	14
26	**1Bl**	4-FC_6H_4	*i*Pr	32	4.42	20	15	10	19
27	**1Bm**	4-ClC_6H_4	*i*Pr	38 (37[c])	4.40	19	10	11	16
28	**1Bn**	4-CNC_6H_4	*i*Pr	53	4.29	18	14	3	17
29	**1Bo**	4-$NO_2C_6H_4$	*i*Pr	58 (38[c])	4.30	13	16	4	17
30	**1Bp**	3-$MeOC_6H_4$	*i*Pr	34 (28[c])	4.45	6	17	5	22
31	**1Bq**	3-MeC_6H_4	*i*Pr	28	4.44	10	14	5	25
32	**1Br**	3-$NO_2C_6H_4$	*i*Pr	56	4.33	10	15	3	22
33	**1Bs**	3,5-$(NO_2)_2C_6H_3$	*i*Pr	70	4.30	10	14	–	12
34	**1Bt**	2-Thienyl	*i*Pr	11	4.88	8	11	30	49
35	**1Bu**	2-Pyridyl	Me	nd	–	10	–	–	45

[a]Yields determined by ^{1}H NMR; nd—not detected, confirmed by negative Fe^{3+} test.
[b]Not estimated due to overlapping signals.
[c]Isolated yield; characterized in [11].

calculated from the area integration of clearly identifiable resonances of the respective *N*-alkyl protons in ^{1}H NMR spectra of reaction mixtures.

Analysis of the results presented in Table 1 reveals that enlargement of *N*-alkyl substituent in acetohydroxamic acids (**1Aa–c**) and butyrohydroxamic acids (**1Ag–i**) lowers THA **2** yield. It is also interesting to note that *N*-Me HAs usually afforded THAs in lower yields. Among pivalohydroxamic acids only *N*-methyl HA **1Aj** reacts with LR, but it affords solely a mixture of pivaloamide and pivalothioamide. Phenylaceto-(**1Al**), malono-(**1Am**), 2-pyrido-(**1Bu**), *N*-*t*-Bu-(**1Ai, 1Bc**), *N*-phenylhydroxamic acids (**1Ae**, **1Af, 1Bd**) and 4-dimethylaminobenzohydroxamic acid **1Bf** did not produce the corresponding THAs at all. Cinnamohydroxamic acid **1An** gives THA **2An** in only 5% yield. In the case of benzohydroxamic acids, a secondary alkyl group (*i*Pr) constitutes the optimum. *N*-Methyl **1Ba** and *N*-benzyl **1Bb** HAs give lower yields of THAs (ca. 30%), whereas *N*-*t*-Bu HA **1Bc** produces exclusively the corresponding benzamide **3Bc** (92%). This is due to the irreversible formation of the adduct of **1Bc** and AnsPSS; therefore, only deoxygenation was observed in this case. This fact was confirmed by ^{31}P NMR spectroscopy. In the ^{31}P NMR spectrum of the reaction mixture produced by **1Bc** and LR, the signal of the corresponding adduct **1Bc-PSSH** ($\delta_P = 112$ ppm) was the most intensive one during the first stage of the reaction.

From the data in Table 1 one can also see that some HAs can be inactive toward LR. In the case of *N*-isopropyl pivalohydroxamic acid **1Ak**, the steric

hindrance around the carbonyl as well as around the N—OH group is responsible for total inertness. *N*-Methyl 2,4,6-trimethylbenzohydroxamic acid **1Be** gives only the corresponding amide (58%) and no THA or thioamide, which indicates that thionation is impossible in that case because of steric crowding near the carbonyl group.

The increase in yield of amides produced by deoxygenation may also be associated with steric crowding around the *N*-hydroxyl group. Particularly steric compression dominates in the case of *N*-*t*-Bu HAs, where the degree of pyramidization of the nitrogen atom due to the fact that its lone electron pair is not coplanar with the carbonyl moiety is high. Therefore, in *N*-*t*-Bu HAs the N—O bond becomes weaker and the carbonyl oxygen less nucleophilic, which results in shifting the equilibrium of adduct formation to the right (see above). 2-Pyridinohydroxamic acid **1Bu** is deoxygenated exclusively, probably because of existence of a competitive nucleophilic center at the nitrogen atom of the pyridine residue.

As it was demonstrated, the direct thionation method could be useful for *N*-alkyl aceto- and benzohydroxamic acids lacking electron-donating groups in the aromatic ring. Some HAs were shown to fail to undergo thionation due to either steric hindrance (*N*-*t*-Bu-, mesitylhydroxamic acids), significant acidity of α-hydrogens (phenylaceto- and malonohydroxamic acids), presence of an additional nucleophilic center (**1Bu**), or ease of reduction of both HA and THA (*N*-aryl, EDG-substituted benzohydroxamic acids). Therefore, in the case of these HAs direct thionation is completely unfeasible under chosen reaction conditions.

As mentioned before and confirmed in this report, *N*-isopropyl benzohydroxamic acids bearing EWG substituents produce the corresponding THAs with higher yields, which seems quite unexpected in light of previous reports [9]. In the case of electron-rich HAs, the results are very poor (0% for **1Bf**, 15% for **1Bg** and **1Bh**) because of the competing deoxygenation reaction. To evaluate the impact of electronic effects on thionation, a series of ring-substituted *N*-isopropyl benzohydroxamic acids **1Bf–s** was chosen. Correlation of the THA yields (relative to the unsubstituted THA **2Bk**) with Hammett constants (σ and σ^+) of substituents was investigated. Clearly, the yields correlate better with Brown σ^+ substituent constant ($r = 0.95$, $\rho = 0.33$) (Fig. 1) than with σ. Even though linearity is not excellent in general, the Hammett plot does provide useful insights into the reaction mechanism. First, the relatively small magnitude of the reaction constants, ρ, indicates that this reaction is

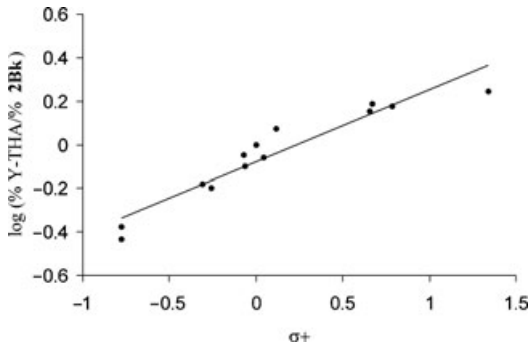


FIGURE 1 Hammett plot of the Y-substituted THA **2Bg–s** relative yield against σ^+ values ($r = 0.95$, $\rho = 0.33$).

only slightly sensitive to change in the electronic nature of substituents in the phenyl ring. Second, the observed dramatic fall of yields of EDG-substituted THAs reflects the more nucleophilic/less acidic nature of EDG-substituted HAs.

It is obvious that THA yields depend on rate differences between two pairs of competitive processes, but as mentioned before, higher electron densities on *N*-hydroxyl group of both HA and THA determine the extent of their deoxygenation (R_1 and R_2).

Very interesting substituent effects were observed in ^{1}H NMR spectra of *N*-isopropyl derivatives under investigation. Good correlation (negative slope) was found for methine proton NMR chemical shifts of *para*-substituted HAs **1Be–r**, and the effect of substituents was compared to those obtained for the corresponding THAs **2Be–r**, amides **3B**, and thioamides **4B**. Surprisingly, the respective shifts for 4-substituted *N*-isopropyl benzamides **3B** and thiobenzamides **4B** are almost insensitive to substituent effects (Fig. 2). On the contrary, we previously showed that ^{15}N chemical shifts of THAs **2B** and HAs **1B** are also linearly correlated with

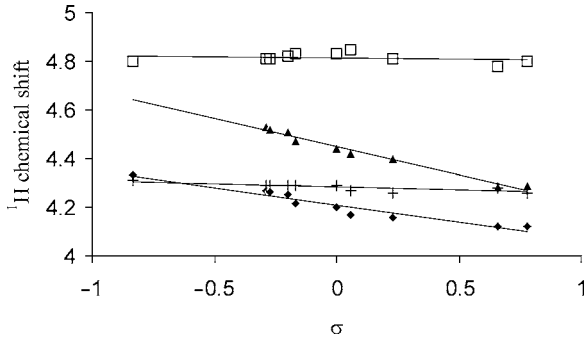


FIGURE 2 Hammett plot of the methine proton chemical shift values for HAs **1Bg–s** (♦, $r = 0.9652$, slope = −0.141 ppm) and for the respective: A (+), THAs **2Bg–s** (▲, $r = 0.9883$, slope = −0.231 ppm), and TA (□) against σ values.

the Brown constant, but the substituent effects are two times smaller than those for the corresponding thioamides and amides [11]. It is well known that in solution HAs and THAs exist as mixtures of *Z* and *E* isomers. It was confirmed that in the cases of the investigated HAs and THAs one isomer usually dominates. At room temperature, ^{1}H NMR spectra of HAs **1B** and THAs **2B** consist of averaged signals of both isomers [11], whereas in spectra of aliphatic HAs, e.g., **1Ag–I**, two resonances are often seen. The position of averaged signals obtained at room temperature for aromatic derivatives **1B** and **2B** depends mainly on the both isomers population. Because the isomers ratio reflects the difference in acidity of various substituted compounds under investigation and THAs are stronger acids than HAs, the observable influence of substituents on methine proton chemical shift is greater in the case of THAs **2B**.

Although the initial intent was to determine the relative rates of all the above-mentioned processes (Scheme 1), we were able to determine only the relative rates of the two subsequent reactions (k_{R_2} and k_{T_2}). Attempts to study the kinetics of HAs reduction and HAs thionation (k_{R_1} and k_{T_1}) were unsuccessful. One must consider that the results obtained in this way can only approximate the observed reactivity of LR toward HAs. The *n*-Bu_3P/Ph_2S_2 system, very similar to LR as far as reactivity is concerned, used by Barton and coworkers for reduction of *N*-methylbenzohydroxamic acid **1Ba** [12], was found to be totally inert toward *N*-isopropylhydroxamic acid **1Bk**. On the other hand, $TiCl_3$, which efficiently splits N—O bonds in *N*-methyl phenylacetohydroxamic acids [13], was probably too reactive and produced a nearly equimolar mixture of the corresponding 4-methoxybenzamide **3Bh** and 4-nitrobenzamide **3Bo**. One could speculate that LR action may be similar to that of $TiCl_3$ in reduction of HAs. However, everything indicates that the mode of action of $TiCl_3$ is quite different from that of LR. On the other hand, so far no other efficient chemoselective reagent for thionation of HAs is known besides LR. Therefore, we decided to involve *N*-methoxy derivatives **8Bh** and **8Bo** to study the kinetics of thionation (T_1). Surprisingly, in this case it was found that LR did not significantly differentiate substrates with EDG and EWG substituents. In this way, it was confirmed again that the hydroxyl group in HAs plays a crucial role in their reaction with LR.

Fortunately, HAs are much more reactive toward LR than THAs and amides. Therefore, addition of LR in a stoichiometric amount yields the THA almost intact for further reduction and both subsequent undesired processes (T_2 and R_2) have only a minuscule impact on its yield.

TABLE 2 Effect of Substituents on 4-Y Substituted Benzothiohydroxamic Acids **2B** and Benzamides **3B** Reactivity (*k* Relative Rates)

Y	k_{R_2}	k_{T_2}	k_{T_2}/k_{R_2}
OMe	1.80[a]	1.21	0.57
H	1	1	1.52
NO_2	0.22	0.70	1.92

[a]For **2Bh** + **2Bk** → **4Bh** + **4Bk** $k_{R_{2(OCH_3)}}$ = [**4Bh**]/[**4Bk**].

Despite these observations, it seemed interesting how the rates of both above-mentioned subsequent processes can influence THA yield depending on substituent. Hence, relative rates of k_{T_2} and k_{R_2} for pairs of different substituted benzamides **3B** and benzothiohydroxamic acids **2B** were measured. In addition, k_{T_2}/k_{R_2} ratios for pairs of benzamides **3B** and THAs **2B** with the same substituents were determined as well. Appropriate competition experiments showed that the reaction rates increased with electron-donating abilities of the substituent. Consequently, it was found that 4-methoxy-substituted THA **2Bh** is deoxygenated eight times faster than 4-nitro-substituted one **2Bo**. Its reduction is two times faster than thionation of the corresponding benzamide **3Bh**. THA with 4-nitro substituent **2Bo** is reduced two times slower than the corresponding benzamide **3Bo** is thionated. In the case of benzamides, 4-methoxybenzamide **3Bh** is thionated 1.73 times faster than 4-nitrobenzamide **3Bo** (Table 2).

CONCLUSION

Strictly speaking, the more electron-donating the substituent and the greater the steric hindrance, the lower the THA yield. The observed trend in thionation of HAs is opposite to that reported previously for esters [9] and found in the present work in the case of amides. In the case of EDG-substituted HAs deoxygenation to the corresponding amide **3** predominates. EWG-substituted HAs are prone to thionation due to relatively strong N—O bond and lower nucleophilicity. Thus, similarly to thioacylation with *S*-thioacyldithiophosphates, also the proposed method of direct thionation using LR is inefficient for obtaining EDG THAs and those with hindered thioacyl residues. Still, some products could be easily isolated, albeit in low yields (e.g., **2Bh**). This method does not work for *N*-phenylhydroxamic acids or for those with a bulky *N*-substituent (*t*-Bu). Correlation with the Brown substituent constant was found for the yield of 4-substituted *N*-isopropylbenzohydroxamic acids (positive slope) and for

chemical shifts of their methine protons (negative slope), while ^{1}H chemical shifts for the respective amides and thioamides were observed to be insensitive to substituent effects. Attempts were made to measure the relative rates of the two subsequent processes, THA deoxygenation (k_{R_2}) and amide thionation (k_{T2}). Kinetic studies showed that deoxygenation of EDG-substituted THA is also faster than thionation of the corresponding benzamide but both undesired processes (T_2 and R_2) have only a minuscule impact on THA yield.

EXPERIMENTAL

General Remarks

NMR spectra were recorded in $CDCl_3$ on Varian 200 and 500 MHz spectrometers with TMS as internal standard. Coupling constants are reported in Hertz. IR spectra were obtained using a Bruker IFS66 spectrometer in KBr. MS spectra were measured with an AMD 604 mass spectrometer (AMD Intectra GmbH, Germany).

THF was distilled from potassium/benzophenone ketyl. Commercial LR (Lancaster) was recrystallized from chlorobenzene prior to use. Almost all aroyl chlorides were commercial compounds (Lancaster) with the exceptions of 4-benzyloxybenzoyl chloride that was prepared from the corresponding acid and oxalyl dichloride. *N*-Isopropyl hydroxylamine hydrogen oxalate was prepared from 2-methylnitroethane by reduction using zinc powder. *N*-Methyl-, *N-tert*-butyl- and *N*-benzylhydroxylamine hydrochlorides were obtained from Aldrich. Hydroxamic acids **1Aa** [14], **1Ab** [15], **1Ac** [16], **1Ad** [17], **1Ae–1Af** [18], **1Aj–1Ak** [19], **1Al** [20], **1Am** [21], **1An** [22], **1Ba** [23], **1Bb–1Bc** [24], **1Bd** [25], **1Be** [26], **1Bf** [8], **1Bh** [8], **1Bk** [7], **1Bo** [8], and **1Bu** [27] are known compounds and were synthesized according to general procedure described below. Thiohydroxamic acids **2Bh, 2Bi, 2Bm, 2Bo**, and **2Bp** were prepared and characterized previously [11]. Benzamides **3Bh, 3Bo** [28] and thioamides **4Bh** [29], **4Bo** [30] are already known compounds. Benzamides were made by benzoylation of isopropylamine (in excess) and thioamides by thionation of the corresponding amides with LR in THF at room temperature.

All reactions with LR were performed under argon in flame-dried flasks equipped with a stirring bar and a rubber septum.

THAs were detected on developed chromatograms by spraying with 1% methanolic $FeCl_3$ solution. THAs gave black spots as compared to HAs, which showed a violet coloration.

N-Alkyl hydroxamic acids **1Aa–1Bu** *typical procedure*. A stirred suspension of *N*-alkyl- or *N*-arylhydroxylamine salt (12 mmol) in CH_2Cl_2 (50 mL) containing triethylamine (3.04 mL, 20 mmol) was cooled in an ice bath and treated with the appropriate acyl chloride (10 mmol) in CH_2Cl_2 (10 mL) added dropwise over 1 h. After an additional 2 h at room temperature, the mixture was washed with water (2 × 15 mL), 1 M HCl (10 mL), water, and brine, and dried with $MgSO_4$. The solvent was evaporated, and the crude HA was crystallized or purified by radial chromatography.

N-Methylbutyrohydroxamic acid **1Ag**. Yield 55%, a colorless oil; δ_H (*Z*/*E* isomer = 1:1.6): 0.96 (3H, m, C*H*$_3$CH$_2$), 1.63 and 1.67 (2H, 2 × m, C*H*$_2$CH$_3$), 2.31 and 2.46 (2H, 2 × t, C*H*$_2$CH$_2$CH$_3$), 3.24 and 3.37 (3H, 2 × s, N-C*H*$_3$), 7.56 (1H, br s, O*H*); δ_C 13.8 and 14.1 (*C*H$_3$CH$_2$), 18.4 and 18.9 (CH$_3$*C*H$_2$), 33.5 and 34.4 (*C*H$_2$CO), 36.3 (N*C*H$_3$), 167.9 and 175.1 (C=O); HRMS: calcd for $C_5H_{11}NO_2$ 117.07898; found 117.07932.

N-Isopropylbutyrohydroxamic acid **1Ah**. Yield 84%, a colorless oil; δ_H (*Z*/*E* isomer = 2.6: 1): 0.88 (3H, t, C*H*$_3$CH$_2$), 1.07 and 1.24 (6H, 2 × d, C*H*$_3$CH), 1.56 (2H, m, C*H*$_2$CH$_3$), 2.22 and 2.38 (2H, 2 × t, C*H*$_2$CH$_2$CH$_3$), 4.12 and 4.60 (1H, 2 × spt, N-C*H*), 8.80 (1H, br s, O*H*); δ_C 13.7 and 14.0 (*C*H$_3$CH$_2$), 18.3 and 18.5 (CH$_3$*C*H$_2$), 19.0 and 20.0 (*C*H$_3$CH), 34.8 and 36.2 (*C*H$_2$CO), 46.4 and 47.2 (N*C*HCH$_3$), 174.4 and 177.7 (C=O); HRMS: calcd for $C_7H_{15}NO_2$ 145.11028; found 145.11065.

N-tert-Butylbutyrohydroxamic acid **1Ai**. Yield 48%, a colorless oil, δ_H (*Z*/*E* isomer = 1:1.1): 0.78 and 0.83 (3H, 2 × t, C*H*$_3$CH$_2$), 1.00 and 1.27 (9H, 2 × s, C*H*$_3$C), 1.45 and 1.55 (2H, m, C*H*$_2$CH$_3$), 2.21 and 2.28 (2H, 2 × t, C*H*$_2$CH$_2$CH$_3$), 8.90 (1H, br s, O*H*); δ_C 13.7 and 13.9 (*C*H$_3$CH$_2$), 18.1 and 18.5 (CH$_3$*C*H$_2$), 26.4 and 27.6 (C*C*H$_3$), 34.5 and 36.9 (*C*H$_2$CO), 55.7 and 60.8 (N*C*CH$_3$), 173.5 and 175.9 (C=O); HRMS: calcd for $C_8H_{17}NO_2$ 159.12593; found 159.12544.

N-Isopropyl-4-benzyloxybenzohydroxamic acid **1Bg**. Yield 73%, m.p. 123–125°C (benzene–cyclohexane); ν_{max}/cm^{-1} 3113 (OH), 1607 and 1586 (C=O); δ_H 1.31 (6H, d, CHC*H*$_3$), 4.27 (1H, spt, C*H*CH$_3$), 5.11 (2H, s, OC*H*$_2$Ph), 7.01 (2H, d, $J = 9$, H-3/5), 7.42 (5H, m, OCH$_2$*Ph*), 7.48 (2H, d, $J = 9$, H-2/6), 8.40 (1H, br s, O*H*); δ_C 19.6 (*C*H$_3$CH), 52.7 (CH$_3$*C*H), 70.0 (O*C*H$_2$Ph), 114.7 (C-3/5), 125.1 (C-1), 129.4 (C-2/6), 160.7 (C-4), 127.4, 128.2, and 128.6 (OCH$_2$*Ph*), 167.1 (C=O). Found: C, 71.82; H, 6.80;

N, 4.64%. $C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.71; N, 4.91%.

N-Isopropyl-4-tert-butylbenzohydroxamic acid **1Bi**. Yield 69%, m.p. 103–105°C (ethanol–water); ν_{max}/cm^{-1} 3159 (OH), 1609 and 1593 (C=O); δ_H 1.31 (6H, d, CHCH_3), 1.34 (9H, s, ArBu^t), 4.26 (1H, spt, CHCH$_3$), 7.45 (4H, s, ArH), 8.60 (1H, br s, OH); δ_C 19.7 (CH$_3$CH), 31.1 (ArCCH$_3$), 34.8 (ArCCH$_3$), 52.4 (CH$_3C$H), 125.5 (C-3/5), 127.3 (C-2/6), 129.9 (C-1), 154.0 (C-4), 166.9 (C=O). Found: C, 71.06; H, 9.17; N, 5.87%. $C_{14}H_{21}NO_2$ requires: C, 71.46; H, 8.99; N, 5.95%.

N-Isopropyl-4-methylbenzohydroxamic acid **1Bj**. Yield 88%, m.p. 115°C (benzene–hexane); ν_{max}/cm^{-1} 3187 (OH), 1612 and 1591 (C=O); δ_H 1.28 (6H, d, CHCH_3), 2.39 (3H, s, ArCH_3), 4.23 (1H, spt, CHCH$_3$), 7.23 (2H, d, $J = 9$, H-3/5), 7.39 (2H, d, $J = 9$, H-2/6), 8.55 (1H, br s, OH); δ_C 19.6 (CH$_3$CH), 21.4 (ArCH$_3$), 52.5 (CH$_3C$H), 127.5 (C-2/6), 129.2 (C-3/5), 130.0 (C-1), 141.0 (C-4), 167.0 (C=O). Found: C, 68.61; H, 7.96; N, 7.10%. $C_{11}H_{15}NO_2$ requires: C, 68.37; H, 7.82; N, 7.25%.

N-Isopropyl-4-fluorobenzohydroxamic acid **1Bl**. Yield 82%, m.p. 97°C (benzene–hexane); ν_{max}/cm^{-1} 3200 (OH), 1604 and 1584 (C=O); δ_H 1.27 (6H, d, CHCH_3), 4.22 (1H, spt, CHCH$_3$), 7.07 (2H, dd, $J = 8.8$ and 8.9, H-3/5), 7.48 (2H, dd, $J = 8.8$ and 5.3, H-2/6), 8.62 (1H, br s, OH); δ_C 19.5 (CH$_3$CH), 52.5 (CH$_3C$H), 115.6 (d, $J = 22$, C-3/5), 129.8 (d, $J = 9$, C-2/6), 129.2 (C-1), 163.9 (d, $J = 251$, C-4), 166.2 (C=O). Found: C, 61.25; H, 6.25; N, 6.94%. $C_{10}H_{12}NO_2F$ requires: C, 60.90; H, 6.13; N, 7.10%.

N-Isopropyl-4-chlorobenzohydroxamic acid **1Bm**. Yield 73%, m.p. 123–124°C (benzene–hexane); ν_{max}/cm^{-1} 3152 (OH), 1608 and 1592 (C=O); δ_H 1.31 (6H, d, CHCH_3), 4.19 (1H, spt, CHCH$_3$), 7.35–7.50 (4H, m, ArH), 8.50 (1H, br s, OH); δ_C 19.5 (CH$_3$CH), 52.1 (CH$_3C$H), 128.7 and 128.9 (C_{Ar}-H), 131.4 (C-1), 136.7 (C-4), 165.8 (C=O). Found: C, 56.23; H, 5.63; N, 6.31%. $C_{10}H_{12}NO_2Cl$ requires: C, 56.21; H, 5.66; N, 6.56%.

N-Isopropyl-4-cyanobenzohydroxamic acid **1Bn**. Yield 61%, m.p. 124–126°C (benzene–hexane); ν_{max}/cm^{-1} 3207 (OH), 2233 (CN), 1613 and 1600 (C=O); δ_H 1.32 (6H, d, CHCH_3), 4.12 (1H, spt, CHCH$_3$), 7.62 (2H, d, $J = 9$, H-2/6), 7.78 (2H, d, $J = 9$, H-3/5); δ_C 19.4 (CH$_3$CH), 52.2 (CH$_3C$H), 113.6 (C-4), 117.3 (CN), 128.2 (C-2/6), 132.3 (C-3/5), 137.6 (C-1), 164.6 (C=O). Found: C, 64.81; H, 5.91; N, 13.40%. $C_{11}H_{12}N_2O_2$ requires: C, 64.69; H, 5.92; N, 13.40%.

N-Isopropyl-3-methoxybenzohydroxamic acid **1Bp**. Yield 96%, m.p. 104–105°C (benzene–hexane); ν_{max}/cm^{-1} 3116 (OH), 1604 and 1574 (C=O); δ_H 1.31 (6H, d, CHCH_3), 3.84 (3H, s, OCH_3), 4.23 (1H, spt, CHCH$_3$), 7.02 (1H, dt, $J = 8$ and 1.5, H-4), 7.04 (1H, t, $J = 1.5$, H-2), 7.06 (1H, dt, $J = 8$ and 1.5, H-6), 7.35 (1H, t, $J = 8$, H-5), 8.40 (1H, br s, OH); δ_C 19.7 (CH$_3$CH), 52.5 (CH$_3C$H), 55.4 (ArOCH_3), 112.8 (C-2), 116.7 (C-4), 119.6 (C-6), 129.7 (C-5), 134.0 (C-1), 159.6 (C-3), 166.2 (C=O); HRMS: calcd for $C_{11}H_{15}NO_3$ 209.10519; found 209.10424.

N-Isopropyl-3-methylbenzohydroxamic acid **1Bq**. Yield 76%, m.p. 61–62°C (benzene–hexane); ν_{max}/cm^{-1} 3140 (OH), 1613 and 1577 (C=O); δ_H 1.29 (6H, d, CHCH_3), 2.38 (3H, s, ArCH_3), 4.20 (1H, spt, CHCH$_3$), 7.23–7.33 (4H, m, Ar H), 8.45 (1H, br s, OH); δ_C 20.3 (CH$_3$CH), 22.0 (ArCH$_3$), 53.0 (CH$_3C$H), 125.0 (C-6), 128.7 (C-2), 129.0 (C-5), 132.1 (C-4), 133.4 (C-1), 139.2 (C-3), 167.3 (C=O); HRMS: calcd for $C_{11}H_{15}NO_2$ 193.11028; found 193.11116.

N-Isopropyl-3-nitrobenzohydroxamic acid **1Br**. Yield 80%, m.p. 96°C (benzene–hexane); ν_{max}/cm^{-1} 3171 (OH), 1602 and 1579 (C=O), 1536 and 1346 (NO_2); δ_H 1.34 (6H, d, CHCH_3), 4.22 (1H, spt, CHCH$_3$), 7.65 (1H, t, $J = 8$, H-5), 7.86 (1H, dt, $J = 8$ and 1.5, H-6), 8.26 (1H, br s, OH), 8.34 (1H, dt, $J = 8$ and 1.5, H-4), 8.38 (1H, t, $J = 1.5$, H-2); δ_C 20.3 (CH$_3$CH), 52.8 (CH$_3C$H), 123.4 (C-2), 126.0 (C-4), 130.5 (C-5), 134.1 (C-6), 135.3 (C-1), 148.3 (C-3), 166.0 (C=O); HRMS: calcd for $C_{10}H_{12}N_2O_4$ 224.07971; found 224.07984.

N-Isopropyl-3,5-dinitrobenzohydroxamic acid **1Bs**. Yield 45%, m.p. 157–159°C (ethyl acetate); ν_{max}/cm^{-1} 3119 (OH), 1614 (C=O), 1543 and 1343 (NO_2); δ_H 1.40 (6H, d, CHCH_3), 4.35 (1H, spt, CHCH$_3$), 8.75 (2H, d, $J = 2$, H-2/6), 9.16 (1H, t, $J = 2$, H-4); δ_C ($CDCl_3$–MeOD 2:1) 18.3 (CH$_3$CH), 48.9 (CH$_3C$H), 119.9 (C-4), 128.8 (C-2/6), 138.6 (C-1), 148.3 (C-3/5), 165.0 (C=O); HRMS: calcd for $C_{10}H_{11}N_3O_6$ 269.06479; found 269.06394.

N-Isopropyl-2-thienohydroxamic acid **1Bt**. Yield 90%, m.p. 103–105°C (chloroform–hexane); δ_H 1.31 (6H, d, CHCH_3), 4.73 (1H, spt, CHCH$_3$), 7.08 (1H, dd, $J = 3.5$ and 5, H-4), 7.52 (1H, dd, $J = 5$ and 1, H-5), 7.68 (1H, dd, $J = 3.5$ and 1, H-3), 7.69 (1H, br s, OH); δ_C 19.3 (CH$_3$CH), 50.9 (CH$_3C$H), 126.9 (C-4), 130.9 (C-5), 132.1 (C-3), 144.0 (C-2), 169.5 (C=O). Found: C, 51.98; H, 5.84; N, 7.31%. $C_8H_{11}NO_2S$ requires: C, 51.87; H, 5.99; N, 7.56%.

N-Isopropyl-4-methoxybenzamide **3Bh**. Yield 76%, m.p. 119–120°C [28] 120°C); δ_H 1.25 (6H, d, CHCH_3), 3.83 (3H, s, OCH_3), 4.27 (1H, spt, CHCH$_3$), 6.00 (1H, br s, NH), 6.89 (2H, d, $J = 9$, H-3/5), 7.73 (2H, d, $J = 9$, H-2/6); δ_C 22.2 (*C*H$_3$CH), 41.1 (CH$_3$*C*H), 54.7 (OCH$_3$), 112.9 (C-3/5), 126.5 (C-1), 127.9 (C-2/6), 161.2 (C-4), 165.5 (C=O).

N-Isopropyl-4-nitrobenzamide **3Bo**. Yield 63%, m.p. 157–158°C [28] 157–158°C); δ_H 1.30 (6H, d, CHCH_3), 4.31 (1H, spt, CHCH$_3$), 6.00 (1H, br s, NH), 7.92 (2H, d, $J = 9$, H-2/6), 8.28 (2H, d, $J = 9$, H-3/5); δ_C 23.2 (*C*H$_3$CH), 43.0 (CH$_3$*C*H), 124.6 (C-3/5), 128.6 (C-2/6), 141.1 (C-1), 149.9 (C-4), 165.2 (C=O).

General Procedure for Synthesis of HAs O-Methyl Esters **8Bh** *and* **8Bo**

A suspension of *N*-isopropyl 4-substituted benzohydroxamic acid **1Bh** or **1Bo** (1 mmol), potassium carbonate (0.276 g, 2 mmol), tetrabutylammonium bromide (0.005 g), and methyl iodide (0.19 mL, 3 mmol) was stirred at room temperature. After 16 h, 10 mL of water was added and the mixture was extracted three times with methylene dichloride. The combined organic layers were washed successively with water, saturated $NaHCO_3$ solution, and brine. After drying with $MgSO_4$ the solvent was removed to yield of chromatographically pure methyl ester **8B** as colorless oil.

N-Isopropyl N-methoxy 4-methoxybenzamide **8Bh**. Yield 0.158 g (71%); ν_{max}/cm^{-1} 1660 (C=O); δ_H 1.29 (6H, d, CHCH_3), 3.63 (3H, s, NOCH_3), 3.85 (3H, s, ArOCH_3), 4.52 (1H, spt, CHCH$_3$), 6.90 (2H, d, $J = 8.8$, H3/5), 7.63 (2H, d, $J = 8.8$, H-2/6); δ_C 20.2 (*C*H$_3$CH), 52.5 (CH$_3$*C*H), 52.5 (CH$_3$*C*H), 55.8 (ArO*C*H$_3$), 64.7 (N–O*C*H$_3$), 113.9 (C-3/5), 127.7 (C-1), 130.4 (C-2/6), 161.9 (C-4), 170.5 (C=O); HRMS: calcd for $C_{12}H_{17}NO_3$ 223.12084; found 223.12156.

N-Isopropyl N-methoxy 4-nitrobenzamide **8Bo**. Yield 0.183 g (77%); ν_{max}/cm^{-1} 1657 (C=O), 1524, 1351 (NO_2); δ_H 1.24 (6H, d, CHCH_3), 3.57 (3H, s, NOCH_3), 4.59 (1H, spt, CHCH$_3$), 7.78 (2H, d, $J = 8.8$, H-2/6), 8.27 (2H, d, $J = 8.8$, H3/5); δ_C 20.2 (*C*H$_3$CH), 51.5 (CH$_3$*C*H), 65.4 (N–O*C*H$_3$), 123.9 (C-3/5), 129.3 (C-2/6), 141.7 (C-1), 149.1 (C-4), 168.6 (C=O); HRMS: calcd for $C_{11}H_{14}N_2O_4$ 238.09536; found 238.09662.

Thionation of HAs 1 with LR. To a stirred solution of the appropriate HA 1 (0.2 mmol) in THF (2 mL) LR (0.11 mmol) was added in one portion. After 2 h the reaction mixture was quenched with several drops of water, the solvent was stripped off, and the resulting oil was evaporated three times with $CDCl_3$ before NMR analysis.

Kinetic Studies. Equimolar amounts of two different substituted THAs **2B** or benzamides **3B** or a mixture of THA **2B** and benzamide **3B** with the same substituent (0.2 mmol) in 2 mL of THF were treated with 0.05 mmol of LR at 25°C, and the reaction mixtures were quenched with several drops of water after 5 min. Relative rates were determined from ^{1}H NMR spectra of reaction mixtures (after removal of solvents) on the basis of the thioamides **4B** yield ratio and/or unreacted starting materials yield ratios, respectively.

Reaction of Benzohydroxamic Acid O-Methyl Esters **8Bh** *and* **8Bo** *with LR.* Equimolar amounts of *O*-methyl esters **8Bh** and **8Bo** (0.2 mmol) in 2 mL of THF were treated with 0.05 mmol of LR at 25°C, and the reaction mixtures were quenched with several drops of water after 5 mins. After removal of volatiles, ^{1}H NMR spectrum analysis showed that the residue consisted nearly equal amounts of the unreacted starting materials **8Bh** and **8Bo**.

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