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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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