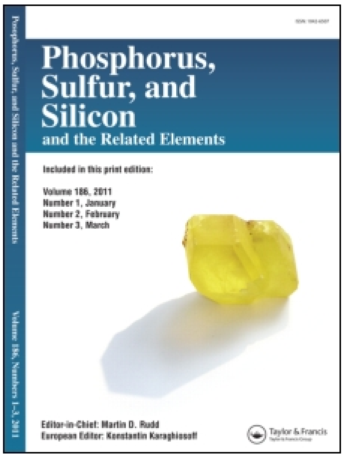

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Synthesis and Structure Determination of Some Monothio- and Dithioimides Derived from Succinic and Glutaric Acids

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A series of novel 5-thioxopyrrolidin-2-ones and 6-thioxopiperidin-2-ones was synthesized using Lawesson's reagent in thionation of the appropriate imides. The NMR data were determined, and in one case the structure assignment was additionally supported by X-ray crystallography.

Keywords Lawesson reagent; regioselectivity; thioamides; thionation reaction

INTRODUCTION

Thiocarboxoamides and thiocarboxoimides are still the subject of intense investigations by organic chemists. They proved to be valuable intermediates in agriculture and medicine.[1,2] Their sophisticated and rich reactivity[3] make them important intermediates in several aspects of synthetic organic chemistry. Thioamides undergo a broad spectrum of chemical transformations, for example the oxidation to carbonyl compounds,[4] the reduction to amines,[5] or conversion to nitriles.[6] Deprotonation of thioamides produces highly reactive anions capable of a variety of condensation reactions[7] as well as Michael-type additions to unsaturated ketones.[8] Thioamides also undergo several types of cyclization reactions, including electrophile-induced additions to olefins[9]

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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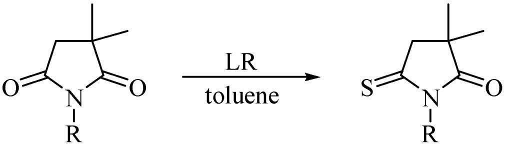
and the Rh(II)-catalyzed reaction of α-diazomethyl vinyl ketones bearing a thioamido substituent.[10] Remarkable chiral memory effect was observed upon a photochemical asymmetric synthesis of a phenyl-bearing quaternary chiral center.[11] In this article, we present the synthesis of a series of thioimides derived from succinic and glutaric acids, along with some spectroscopic and single crystal X-ray data.

RESULTS AND DISCUSSION

In continuation of our ongoing interest in reactivity of amides and imides and the influence of the Ingold–Thorpe effect on tautomeric equilibria, we have recently studied the regioselectivity of the reaction of phenyllithium with differently substituted succinimides and glutarimides.[12] Interestingly, we observed some unexpected differences in the products distribution and their structures in the case of five- and six-membered ring system. Since the thionation reaction, upon treatment of imides with the Lawesson's reagent (LR),[2] is an important method for thioimides formation, we decided to investigate the process for a series of differently substituted imides. Thus, we reacted an equimolar amount of the Lawesson's reagent and appropriate imides in boiling toluene. After completion of the reaction and subsequent column chromatography, the products were recrystallized from the appropriate solvent (see Table I). It is already known that 3,3-dimethylsuccinimide **1** exhibits a high degree of regioselectivity, and under analogous conditions, it produces only 3,3-dimethyl-5-thioxopyrrolidin-2-one **3** in 51% yield[13] (Scheme 1).

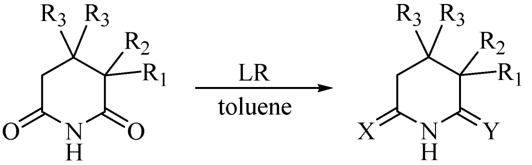


1 R= H
2 R= CH_2Ph

3 R= H
4 R= CH_2Ph

SCHEME 1

Since the replacement of the hydrogen atom in the NH moiety in succinimides sometimes caused a change in regioselectivity,[12] we subjected compound **2** to the thionation reaction. Apparently, steric constraints caused by α-dimethyl group constituted the major factor that affected the mechanism of this reaction, and, as a consequence, the sulfur atom was introduced at the less-hindered side of the molecule to afford exclusively compound **4** in 47% yield. In the glutarimide series, a similar effect was observed. Thus, 3-methylglutarimide **5**, 3,3-dimethylglutarimide **6**, and 3,3,4,4-tetramethylglutarimide **7** were thionated at the C-6 position, giving mono-thioimides **8**, **9**, and **11** in moderate yields (Scheme 2).



5 $R_1= CH_3, R_2=R_3= H$
6 $R_1=R_2= CH_3, R_3= H$
7 $R_1=R_2=R_3= CH_3$

8 $R_1= CH_3, R_2=R_3= H, X= S, Y= O$
9 $R_1=R_2= CH_3, R_3= H, X= S, Y= O$
10 $R_1=R_2= CH_3, R_3= H, X=Y= S$
11 $R_1=R_2=R_3= CH_3, X= S, Y= O$

SCHEME 2

Surprisingly, in the case of compound **6**, the double thionation was also observed, and compound **10** was formed in 23% yield together with the monothio derivative **9** (52% yield).

The structures of all new compounds were derived on the basis of their NMR (^{1}H and ^{13}C) spectra and MS measurements. The differentiation between possible regioisomers of monothio compounds is based on the strong deshielding effect of the C=S group seen in the ^{13}C NMR spectra.[13] Moreover, in the case of the tetramethylderivative **11**, we were able to grow single crystals suitable for an X-ray study that served as unambiguous proof for its structure (Figure 1).

As is shown in the Figure 1, the independent part of the unit cell consists of two molecules differing slightly in their conformation and molecular geometry. The centrosymmetry-related molecules denoted with "un-primed" numbers are bonded through N-H· · ·O hydrogen bonds to form dimers, which are arranged in sheets perpendicular to the *a*-axis and intersecting it at 0, 0, 0 and 1, 0, 0. They are separated by sheets of "primed" molecules, which form N-H· · ·S hydrogen bonds with the neighbor "un-primed" molecules. The crystal packing is depicted in Figure 2.

EXPERIMENTAL

The NMR spectra were recorded with a Varian Unity Plus spectrometer operating at 200 MHz for ^{1}H NMR and at 50 MHz for ^{13}C. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm)

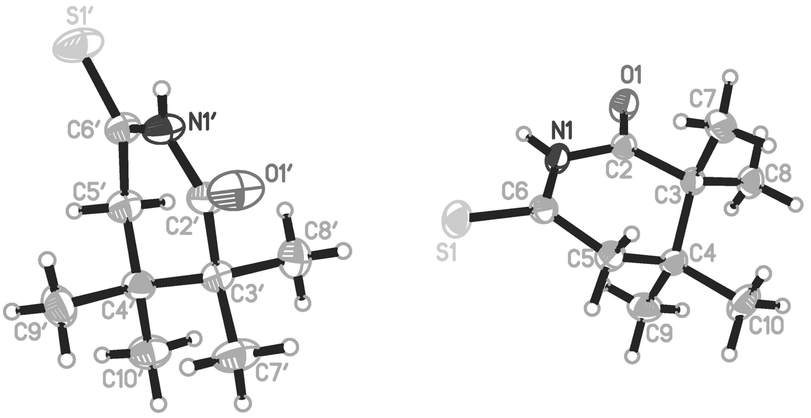


FIGURE 1 Molecular structure of compound **11** in the crystal, independent part of the unit cell; thermal ellipsoids are drawn at 50% probability level.

relative to TMS. Mass spectra were recorded with a LCT Micromass apparatus. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized using UV light or iodine vapor. Column chromatography was carried out using Silica Gel 60 (230–400 mesh,

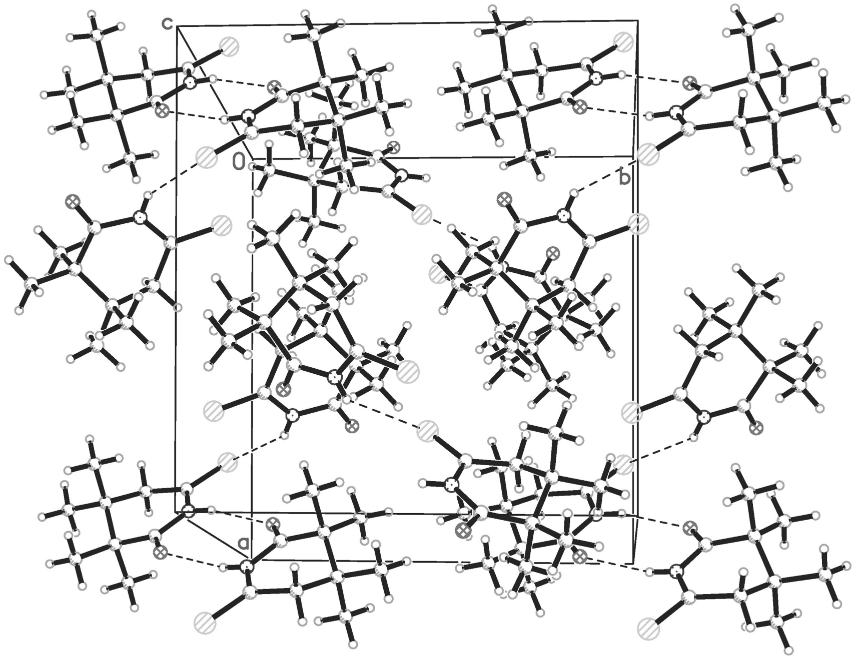


FIGURE 2 The crystal packing of compound **11**.

TABLE I Spectroscopic Data and Physical Properties of Compounds 4 and 8–11[$]

	Mp [°C] (solvent)	Yield [%]	ES MS m/z	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm)
4	51–52 (ether/hexane)	47	$[M+H]^+ = 234$; $[M+Na]^+ = 256$	1.29 (s, 6H, CH_3); 2.99 (s, 2H, CH_2); 5.07 (s, 2H, CH_2Ph); 7.28 (m, 5H, arom-H)	25.3; 40.5; 45.7; 54.9; 128.0; 128.7; 128.9; 135.4; 184.2; 208.9
8	yellow oil	43	$[M+H]^+ = 144$; $[M+Na]^+ = 166$	1.31 (d, $J = 6.8$ Hz, 3H); 2.03 (m, 2H, CH_2); 2.81 (m, 2H, CH_2); 3.28 (m, 1H, CH); 9.34 (br s, 1H, NH)[#]	15.6; 27.8; 36.3; 40.6; 179.6; 208.9
9	60–61 (ether/hexane)	52	$[M+H]^+ = 158$; $[M+Na]^+ = 180$	1.31 (s, 6H, CH_3); 1.87 (t, $J = 6.5$ Hz, 2H, CH_2); 3.08 (t, $J = 6.5$ Hz, 2H, CH_2); 9.78 (br s, 1H, NH)[#]	24.9; 33.5; 37.3; 37.9; 175.2; 208.8
10	70–72 (ether/hexane)	23	$[M+H]^+ = 174$; $[M+Na]^+ = 196$	1.38 (s, 6H, CH_3); 1.85 (t, $J = 6.6$ Hz, 2H, CH_2); 3.10 (t, $J = 6.6$ Hz, 2H, CH_2); 10.80 (br s, 1H, NH)[#]	29.3; 33.3; 38.1; 43.0; 202.9; 213.4
11	129–131 (chloroform)	71	$[M+H]^+ = 186$; $[M+Na]^+ = 208$	1.02 (s, 6H, CH_3); 1.24 (s, 6H, CH_3); 2.96 (s, 2H, CH_2); 9.62 (br s, 1H, NH)[#]	20.3; 23.6; 36.5; 45.0; 52.7; 176.2; 207.0

[$] Satisfactory microanalyses were obtained for all compounds: C ± 0.22, H ± 0.08, N ± 0.08, S ± 0.14%.

[#] Exchangeable with D_2O.

Merck) using mixtures of chloroform/methanol or hexane/ethyl acetate as eluents. Melting points were determined on a Boetius hot-plate microscope and were uncorrected. All solvents used in the reactions were anhydrous. The single crystal X-ray measurements were done with a KUMA KM4 CCD κ-axis diffractometer with point scintillation counter using MoKα radiation. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures using the SHELXS97[14] and SHELXL97[15] programs. In the final structure refinement, the analytical absorption correction was applied to the collected reflections.

Thionation of Imides 2, 5–7: General Procedure

2.5 mmol of the appropriate imide[12] and 2.5 mmol (1.01 g) of the Lawesson's reagent in 200 mL of toluene were refluxed under argon atmosphere for ca. 1.5 h. The progress of the reaction was monitored by TLC. The solution was cooled to ambient temperature and evaporated to dryness. The residue was subjected to column chromatography on silica gel, and the crude product thus obtained was recrystallized (see Table I). The spectroscopic data and physical properties of the products were collected in Table I.

X-ray crystallographic data for **11**: crystal dimensions: $0.6 \times 0.6 \times 0.6$ mm^3, $C_9H_{15}NOS$, M = 185.28, $P2_1/c$ monoclinic space group, a = 13.211(3), b = 12.463(3), c = 12.365(3) Å, $\beta = 101.53(3)^\circ$, Z = 8, $\rho = 1.234$ g/cm^3, T = 293(2) K, λ(MoKα) = 0.71073 Å, μ(MoKα) = 0.280 mm^{-1}, F(000) = 800. 5228 reflections were collected. The final R1 = 0.0495 and wR2 = 0.1447, for 3160 reflections with $I > \sigma(I)$. The detailed structural data were deposited with the Cambridge Crystallographic Data Center under the deposition number CCDC 674008.

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