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Synthesis, Chemistry, and Dynamic NMR Study of New Atropisomeric 4-Dialkylamino-5-chloro-1,2-dithiole-3-thiones

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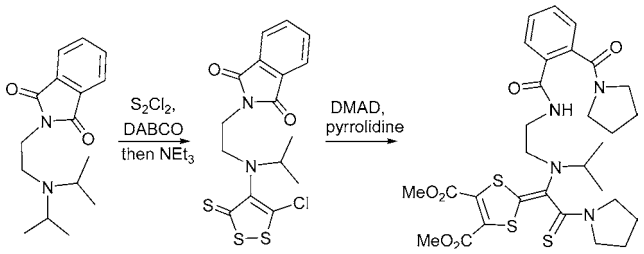
ABSTRACT



Reaction of *N*-(2-phthalimidoethyl)-*N*-alkylisopropylamines and S_2Cl_2 gave atropisomeric (by dynamic NMR) 4-*N*-(2-phthalimidoethyl)-*N*-alkylamino-5-chloro-1,2-dithiole-3-thiones that quantitatively cycloadded to dimethyl or diethyl acetylenedicarboxylate to give a novel class of stable thioacid chlorides, which in turn reacted with 1 or 2 equiv of secondary amines to give thioamides.

Natural and synthetic 1,2-dithiole-3-ones and 3-thiones are now intensely studied because of their unique DNA-targeting antitumor and chemoprotective properties. Leinamycin, a natural 1,2-dithiole-3-one 1-oxide, alkylates DNA at the N7 position of guanine, leading to single-strand cleavage.[1] Oltipraz, [5-(2-pyrazinyl)-4-methyl-1,2-dithiole-3-thione], is currently undergoing clinical trials in China as a chemoprotective agent against liver cancer,[2] and other 1,2-dithiole-3-thiones are being developed as new chemoprotective agents.[1,2b] The sulfuration and chlorination of *N*-(or *S*-)isopropyl groups by disulfur dichloride (S_2Cl_2) constitutes a very fast way to polycyclic 1,2-dithiole-3-thiones,[3] which are also useful materials for the preparation of complex polyheterocyclic systems via 1,3-dipolar cycloadditions.[4] In addition, 1,2-dithiole-3-ones were obtained by trapping the previous reaction intermediates with oxygen nucleophiles.[5] Some of the obtained compounds have been tested by the National Cancer Institute (NCI) at Bethesda in a disease-oriented in vitro anticancer screening program against 60 human tumor cell lines, showing that two dithiolethiones and three dithiolones were moderately active. The bis-dithiolylamine[5a] shown in Figure 1 was one of the most active examples,

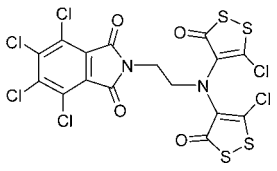


Figure 1.

showing an LC50 of 6×10^{-5} M for some lines of melanoma, colon, renal, and breast cancer. With the aim to

(1) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477−2495.
(2) (a) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461−6473. (b) Timoshenko, V. M.; Bouillon, J. P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2002**, *43*, 5809−5812.
(3) (a) Rees, C. W.; White, A. J. P.; Williams, D. J.; Rakitin, O. A.; Marcos, C. F.; Polo, C.; Torroba, T. *J. Org. Chem.* **1998**, *63*, 2189−2196. (b) Rees, C. W.; White, A. J. P.; Williams, D. J.; Rakitin, O. A.; Marcos, C. F.; Torroba, T. *J. Org. Chem.* **1999**, *64*, 5010−5016. (c) Rees, C. W.; Rakitin, O. A.; Marcos, C. F.; Torroba, T. *J. Org. Chem.* **1999**, *64*, 4376−4380.

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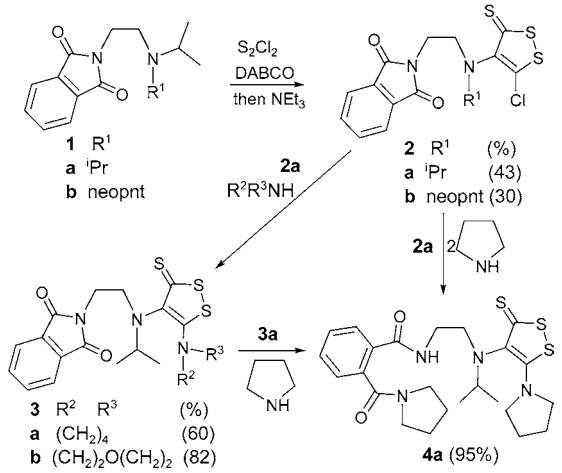
obtain new derivatives with increased antitumor activity we wanted to prepare related compounds bearing the 5-chloro-1,2-dithiole-3-thione group, a rare heterocycle with only one existing report.[6] In this paper we report the selective preparation of stable 4-dialkylamino-5-chloro-1,2-dithiole-3-thiones from tertiary isopropylamines and their unique chemistry as masked thiocarbonyl chlorides.

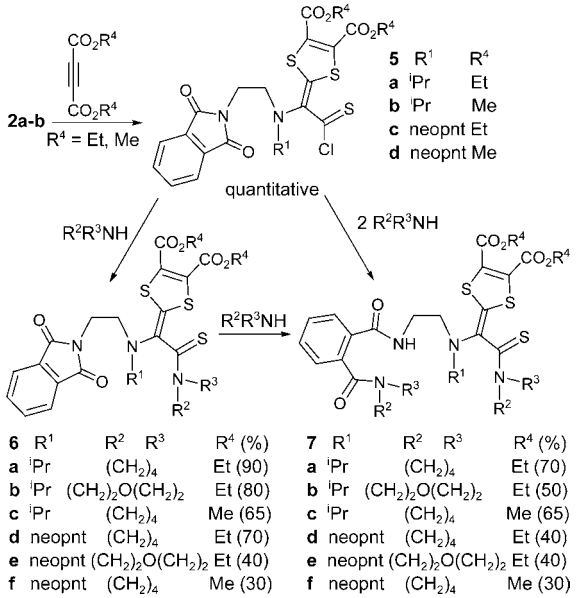
N-(2-Phthalimidoethyl)-*N*-alkylisopropylamines (alkyl = isopropyl, 2,2-dimethylpropyl [neopentyl]) were used as starting materials. *N*-(2-Phthalimidoethyl)diisopropylamine **1a** (1 equiv) and DABCO (4 equiv) in $CHCl_3$ were treated with S_2Cl_2 (5 equiv) at room temperature for 3 days and then the mixture was treated with trietylamine (6.5 equiv) for 2 h at room temperature. Reaction workup and column chromatography of the residue gave **2a** (45%) (Scheme 1).

Scheme 1



Compound **2a** was fully characterized by spectroscopy, microanalysis, and its chemistry. Reaction of **2a** with pyrrolidine or morpholine (1 equiv) gave **3a**,**b** (60−75%), in which only the 5-chloro was selectively substituted. But the reaction of **2a** with an excess of pyrrolidine (2 equiv) gave rise to substitution of the 5-chloro as well as phthalimide opening reaction, to give **4a** (95%). This was a striking result because our previous *N*-phthalimidoethyl heterocycles did not react with amines. When we subjected *N*-neopentyl-*N*-(2-phthalimidoethyl)isopropylamine to the same reaction conditions, we obtained **2b** in lower yield (30%), presumably because of steric hindrance of the neopentyl group. Cycloaddition of **2a**,**b** with dimethyl or diethyl acetylenedicarboxylate (1 equiv) gave quantitatively the rare thioacid chlorides **5a**,**d** as stable solids, fully characterized by spectroscopy (Scheme 2).

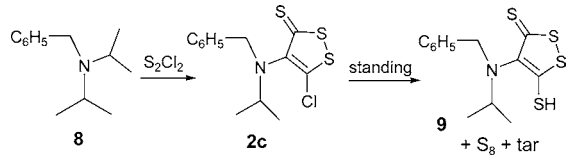
Scheme 2



Thio acid chlorides **5a**−**d** reacted with 1 or 2 equiv of secondary amines to give the polyamides **6a**−**f** (30−90%) and **7a**−**f** (22−60%). Isolation of **5a**−**d** was not necessary for the preparation of polyamides **6a**−**f** and **7a**−**f** that were obtained selectively in one-pot reactions from **2a**,**b** by the sequential addition of reagents at room temperature. In this way, from simple isopropylamines **1a**,**b**, polyamides **7a**−**f** were obtained in only two reaction steps in yields up to 41%.

The reaction could be extended to other substrates, but the obtained products were not sufficiently stable to have synthetic utility. For instance, reaction of *N*-benzyldiisopropylamine **8** with S_2Cl_2 in similar conditions gave **2c** (Scheme 3) (MS EI, M^+ 315, 45%) that, on standing for a few days,

Scheme 3



spontaneously converted into the 3-thiohydroxy derivative **9** (HRMS EI, M^+ 313.010, 25%, $C_{13}H_{15}NS_4$ requires 313.009), in addition of some tar (baseline on TLC) and sulfur.

The reaction of isopropylamines and S_2Cl_2 has probably a wider scope but the unstable nature of many 4-amino-5-chloro-1,2-dithiole-3-thiones has constituted a limit that has kept these compounds hitherto unknown. The remarkable stability of **2a** is probably due to dipole−dipole interactions between the electron-rich 1,2-dithiole-3-thione ring and the electron-poor phthalimido group. This compound showed diastereomeric preferred conformations studied by dynamic

(4) (a) Barriga, S.; Fuertes, P.; Marcos, C. F.; Miguel, D.; Rakitin, O. A.; Rees, C. W.; Torroba, T. *J. Org. Chem.* **2001**, *66*, 5766−5771. (b) Barriga, S.; Fuertes, P.; Marcos, C. F.; Rakitin, O. A.; Torroba, T. *J. Org. Chem.* **2002**, *67*, 6439−6448.

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(6) Wentrup, G.-J.; Koepke, M.; Boberg, F. *Synthesis* **1975**, 525−526.

NMR of the isopropyl signals. The ^{1}H NMR spectrum of **2a** showed a broad signal at δ 1.2 in deuterated chloroform at room temperature, corresponding to slowly interchanging methyl groups of the isopropyl group. The signal was resolved in a doublet of equivalent methyl groups at 60 °C and in two doublets at −40 °C. The ^{13}C NMR showed a broad signal by δ 22 at room temperature that was resolved into one signal at 60 °C and into two signals at −40 °C.

Figure 2 shows the dynamic behavior of the isopropyl group of **2a** in ^{13}C NMR (left) and simulation of the signals

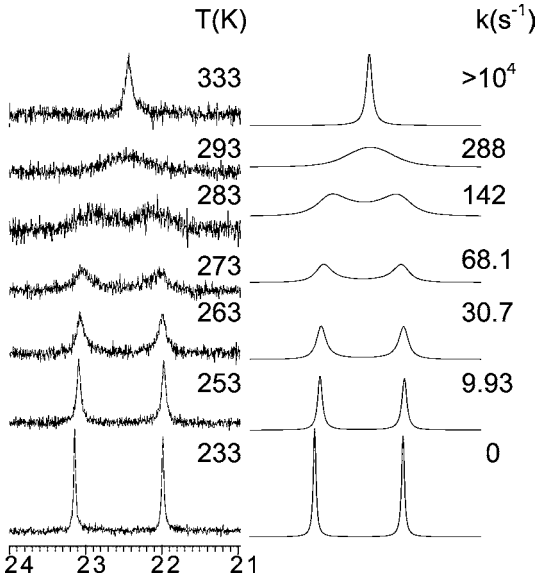

Figure 2.

(right) with gNMR4.0.[7] From these simulations the interchange constants k (s^{-1}) were obtained and plotted as log k/T versus $1/T$, giving a first-order kinetics from which the free energy of transition was calculated to be $\Delta G^{\ddagger} = 13.78 \pm 0.89$ kcal mol^{-1}. A similar value, 13.75 kcal mol^{-1}, was obtained from the Eyring equation at the coalescence temperature $T_c = 285$ K. This energy was ascribed to a slow inversion−rotation process that places the isopropyl group in a diastereotopic environment. Minimization of **2a** followed by conformational search, using in both cases the MNDO/d semiempirical methods, as implemented in HyperChem[8] 5.11 and 6.01, respectively, gave the global minimum **2a(1)** and the nearest minimum **2a(2)** at 0.4 kcal/mol (Figure 3). Interconversion of both minima should happen by 180° rotation of the 1,2-dithiole group, but the barrier was found too high (64.69 kcal mol^{-1}) (rotation of the phthalimidoethyl group was found also very high, 29.75 kcal mol^{-1}). The C−N−C angles[9] were 117.1°, 121.5°, and 118.1° by MNDO/

(7) Budzelaar, P. H. M., Adept Scientific Plc, Amor Way, Letchworht, Herts, SG6 1ZA UK.

(8) Hypercube, Inc., 1115 NW 4th Street, Gainesville, FL 32601.

(9) Similar values of 124.1°, 116.1°, and 116.0° for the C−N−C angles were experimentally found (X-ray diffraction) for a related chlorodithiolone in ref 5a.

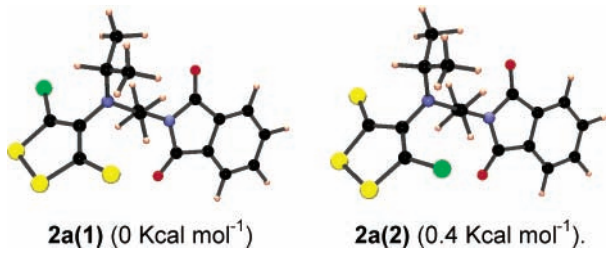

Figure 3. (Left) **2a(1)** (0 kcal mol^{-1}) and (right) **2a(2)** (0.4 kcal mol^{-1}).

d, so the inversion barrier of nitrogen should be very low and the nitrogen could be considered as planar. Therefore the source of the atropisomerism is the high barrier to rotation of the bond between the dithiole ring and nitrogen. This creates an enantiotopic environment for the other nitrogen substituents. The individual methyl groups of the isopropyl group thus become diastereotopic in all conformations of the group. The rotation of the isopropyl group only appears to exchange the methyl groups because the chemical shift difference between the diastereotopic environment of the corresponding methyl groups on the two principal conformers is very small. (There are in principle four methyl environments or eight if nitrogen inversion is counted.) Both calculated minima should coexist at room temperature, giving similar chemical shifts in NMR.

Rotation of the isopropyl group in **2a(1)** gave a potential plot showing a maximum (10.71 kcal mol^{-1}) corresponding to **2a(3)**, which agreed with the experimental value (Figure 4). **2a(3)** showed a steric interaction between the isopropyl group and the chlorine atom of the 1,2-dithiole group.

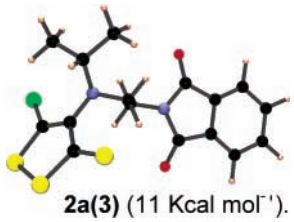

Figure 4. **2a(3)** (11 kcal mol^{-1}).

A 2D plot of potential energy as a function of the dihedral angles (isopropyl)H−C−N−C(dithiole) and (isopropyl)C−N−C−C(ethyl) is shown in Figure 5. It shows a uniform barrier (10.31 kcal mol^{-1}) due to interaction of the isopropyl group with the 1,2-dithiole ring, and two maxima due to interaction of isopropyl and ethyl groups. The maxima can be avoided by correlated rotation of isopropyl and ethyl groups (the large flat region in the center), therefore the measured barrier corresponds to the interaction of isopropyl and dithiole groups where correlated rotation is not possible.

In summary, we have described the synthesis of new potentially antitumor compounds belonging to a very scarce

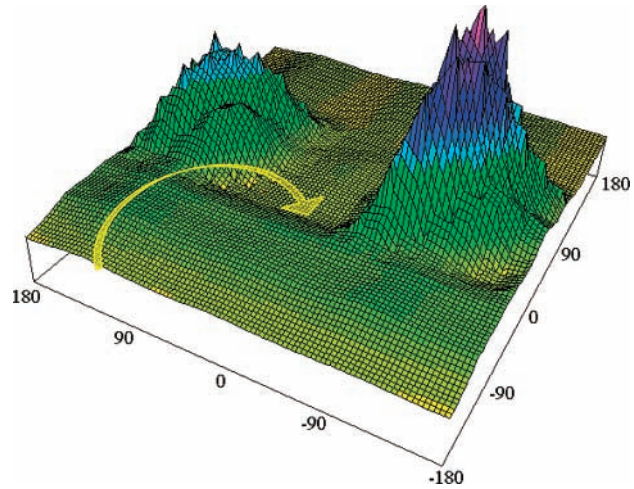

Figure 5.

class of dithioles, the 5-chloro-1,2-dithiol-3-thiones, and showed the rich chemistry of these compounds. In addition, **2a** constitutes a rare example of quirality due to restricted rotation of the dithiole group that gives rise to atropisomers at room temperature. The methyl groups of the isopropyl group only become quasi-equivalent in NMR at high temperatures by fast rotation, but the quirality remains, being **2a** an enantiomeric pair under all circumstances. Some other compounds of the **2a**,**b** to **7a**−**f** series, bearing either isopropyl or neopentyl groups, have shown atropisomers in DNMR studies. The corresponding barriers are now under research.

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Supporting Information Available: Detailed descriptions of experimental procedures, spectra of all new compounds, and X-ray crystallographic files This material is available free of charge via the Internet at http://pubs.acs.org.

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