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Synthesis, reactions and DFT study of tropolone *N*,*N*-dimethylthiocarbamate

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ABSTRACT

A new tropolone derivative namely *O*-(7-oxocyclohepta-1,3,5-trienyl) dimethylthiocarbamate was synthesized from tropolone and *N*,*N*-dimethylthiocarbamoyl chloride and its reactions with lithium halides in acidic media were examined. The product of each lithium halide treatment was identical and identified as *S*-(3-oxocyclohepta-1,4,6-trienyl) dimethylcarbamothioate. Eventually it was converted to 3-mercapto 2,4,6-cycloheptatrien-1-one on treatment with base. DFT calculations at the B3LYP/6-311++G** level were performed on the key elimination step of the mechanism, which was proposed by Ponaras et al. on analogous five-membered ring systems. The experimentally observed regioselectivity was correlated to the calculated activation barriers on five and seven-membered systems in the elimination step such that in both cases, experimentally observed product was favored over the alternative one. Thus, quantum mechanical calculations have provided insights into the synthetic pathway and regioselectivity of the reaction in this study, in comparison to the analogous five-membered system.

1. Introduction

Tropolone is classified as a diosphenol, whose derivatives are known to act as medicaments. Stipitatic acid (**1**),[1] puberulonic acid (**2**),[2] a commercially available drug,[3,4] colchicine (**3**),[5] and hinokitol (**4**)[6] are some examples of tropolone derivatives, which have been isolated from natural products and have antimitotic, antiviral, antibacterial, anticancer effects. Tropolone and its derivatives are also used in some reactions as a starting material for synthetic purposes.[3,7–9] On the other hand, 3-mercaptotropone (3-mercapto 2,4,6-cycloheptatrien-1-one) is a member of troponoid family. While β derivatives are used in some synthesis, to our knowledge, no related record could be found for the 3-mercaptotropone in the literature.[2] Therefore, finding new and easy synthetic methods for obtaining tropolone derivatives is a valuable task in synthetic organic chemistry (Fig. 1).

In this respect, we decided to apply a procedure to replace the enolic hydroxyl group on tropolone with -Cl, -Br, -I after converting to dimethylthiocarbamate derivative (**10**). For this purpose, an earlier study in our group has been utilized with proper modifications for the examination of *N*,*N*-dimethylthiocarbamate of tropolone.[10–12] The synthesis and the reactions of diosphenol thiocarbamates (**6**) with some nucleophiles have been inspected in detail (Scheme 1).[10,11] While replacement of the enolic oxygen of diosphenols (**5**) by chlorine or bromine were achieved by treating the dimethylthiocarbamate of **5** with lithium chloride or bromide in hot acetonitrile/acetic acid (Scheme 1),[11] treatment with lithium iodide gives replacement with hydrogen (Scheme 1).[10] Additionally, several 2-azido- and 2-thiocyanato-2,3-unsaturated cyclohexanones were prepared starting from 1,2-cyclohexanediones by using the same method.[12]

In contrast to previous investigations,[10–12] in this study seven-membered tropolone ring (**9**) was converted to a 3-substituted-2,4,6-cycloheptatrien-1-one (**11**) by following the same experimental procedure.

Newman-Kwart rearrangement is also possible since thiocarbamates is involved in this reaction and an experiment was performed to observe if any related product formed.[13]

As a part of this study, quantum mechanical calculations were performed in order to elucidate the dynamics in the five-membered diosphenols and seven-membered tropolone, which led to different regioselectivity. For this purpose, the key elimination steps are modeled for both reagents by using computational tools to account on the proposed reaction mechanism and to investigate the structural and electronic effects that caused the difference in these two cases.

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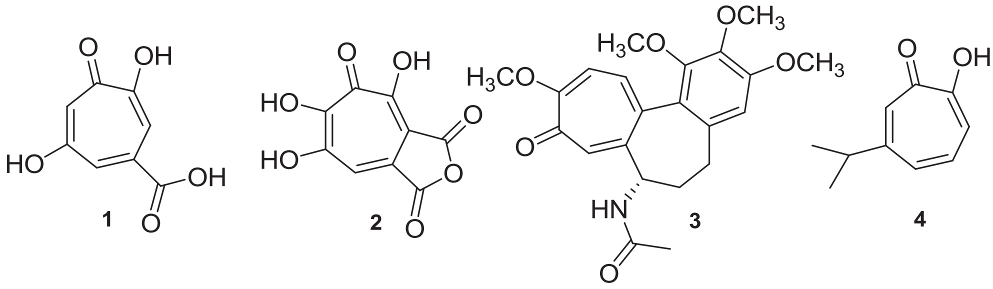
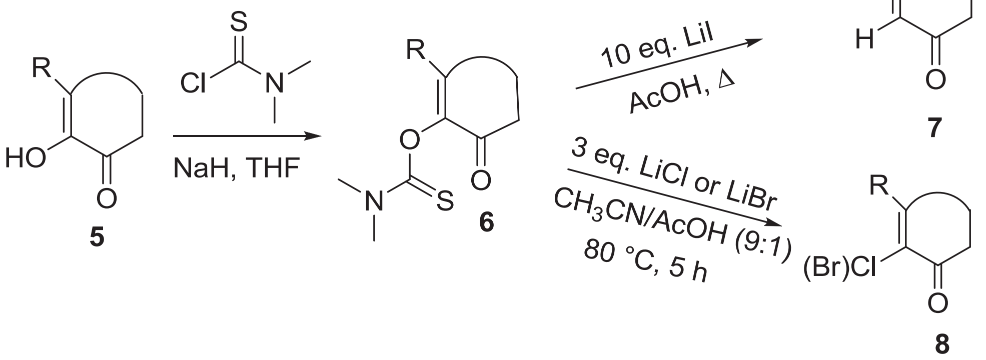


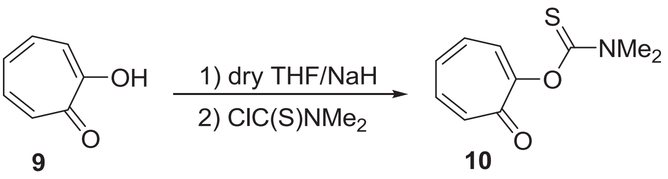
Fig. 1. Derivatives of tropolone.



Scheme 1. Synthesis of diosphenol thiocarbamates with $ClC(S)NMe_2$ and reactions of thiocarbamates with halides.

2. Results and discussion

Tropolone (**9**), an analogous structure to the five- and six-membered diosphenols (**5**), was used as the starting material in our study. As a first step, *N*,*N*-dimethylthiocarbamate (**10**) was synthesized from tropolone with *N*,*N*-dimethylthiocarbamoyl chloride in dry THF (Scheme 2). The product thiocarbamate was treated with LiCl, LiBr and LiI in CH_3CN/CH_3COOH (9:1) solvent system. In contrast to the reactions of the halogens with diosphenol thiocarbamates, an identical compound was obtained from each reaction with halides. This compound was identified as 3-*N*,*N*-dimethylcarbamoylthio derivative (**11**), which is the rearranged product of the 2-*N*,*N*-dimethylthiocarbamate of tropolone (**10**).



Scheme 2. Synthesis of tropolone thiocarbamate with $ClC(S)NMe_2$.

Next, *N*,*N*-dimethylthiocarbamate (**10**) was heated at 250 °C to compare the possible product of the Newman-Kwart reaction[13–15] with our product. Spectroscopic and chromatographic analysis has shown that the product obtained from our procedure (**11**) and the product from Newman-Kwart rearrangement (**12**) were different (Scheme 3).

Product (**11**) was also hydrolyzed in NaOH solution and a new thiol derivative of tropolone (**13**) was obtained (Scheme 4).

The regioselectivity observed in this reaction can be *explained* by the following mechanism (Scheme 5).

Comparison of the product with the products of earlier work has shown a significant difference. In the earlier work,[10–12] enolic oxygen of five- and six-membered diosphenols were replaced by Cl or Br after treating dimethylthiocarbamate with LiCl or LiBr in acidic media. In this work, following the same procedure, led to the substitution at 3-position rather than 2-position of tropolone. To account on this difference, quantum mechanical calculations are performed on both systems.

The proposed pathways for the reactions of **10** and **17** when treated with LiCl (or LiBr), rendering different products, are shown in Scheme 5 and Scheme 6, respectively. The pathway shown in Scheme 6 has been proposed in an earlier report on diosphenols and their hypothesis was confirmed by the observation that the substituents that are reluctant to undergo cyclization (i.e., brosylate, dimethylcarbamate) were unreactive. The difference in products was proposed to stem from the rearrangements followed by elimination products. While **10** leads to **11** possibly from **16**, under the same reaction conditions **17** eliminates dimethylcarbanothioic-*O*-acid (immediately decomposes to dimethyl amine and carbon oxysulfide) from the system. In order to elucidate the product distribution, elimination step was modeled for both **10** and **17** at the B3LYP/6-311++G** level.

For both systems, possible configurations for **16** and **20** including their *Z* and *E* isomers were investigated. Diastereomer analysis has been conducted on both isomers and the minimum energy structures, shown in Fig. 2, were obtained. For both reactions, *E* isomers were found as the minimum energy structures by an energy difference of 2.61 kcal/mol for **16** and 2.91 kcal/mol for **20**. In both cases, the *E* isomers, which have the Cl and dimethylcarbamoylthio substituents in pseudo-axial position are preferred over the *Z* orientation where the pseudo equatorial positioning of the bulky non-bonding orbitals of halogen created steric hindrance. Additionally, in the Z isomer, sulfur, chlorine and