

Novel Thione-Thiol Rearrangement of Dithiocarbonic Acid O-(2,2,6,6-Tetramethylpiperidin-1-yl) Ester in the Context of Controlled Radical Polymerization

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Dedicated to Professor Daniel Belluš on the occasion of his 70th birthday

Abstract: Addition of the lithium salt of N-hydroxy-2,2,6,6-tetramethylpiperidine **10** to carbon disulfide and subsequent methylation affords the rearranged dithiocarbonic acid S-methyl-S'-(2,2,6,6-tetramethylpiperidin-1-yl)-ester **9** rather than the expected xanthate ester S-methyl-O'-(2,2,6,6-tetramethylpiperidin-1-yl)-ester **8**. n-Butylacrylate could be polymerized with the novel compound **9** even though the polymerization was not controlled.

Keywords: Acyloxyamines · Alkoxyamines · Controlled/living radical polymerization · Newman-Kwart rearrangement · Nitroxides · Thione-thiol rearrangement · Thionitroxides

1. Introduction

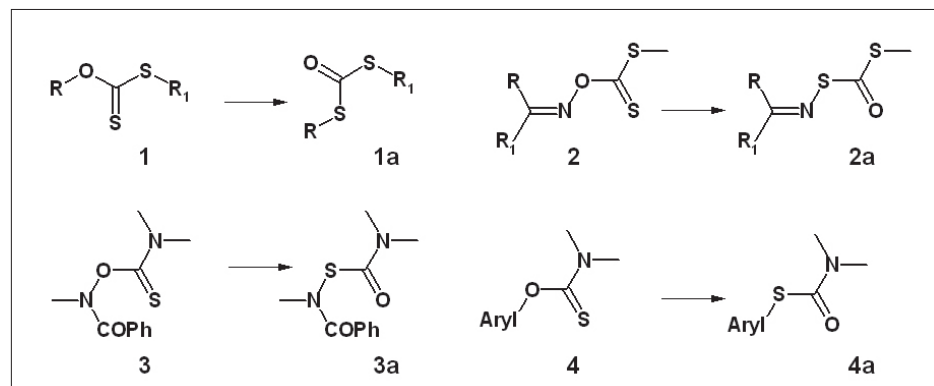
Ciba has a long-standing tradition and leadership in the chemistry of sterically hindered amines. These derivatives of 2,2,6,6-tetramethylpiperidine (TMP) are used as stabilizers to protect synthetic polymers against degradation induced by light and heat. The related nitroxide radicals inhibit the lignin photo-oxidation and thus ensure that wood keeps its natural color and attractive appearance. Recently, the TMP-N-alkoxyamines emerged as environmentally friendly halogen-free flame retardants for plastics.^[1] The next opportunity to further develop the TMP chemistry and expand it beyond the aforementioned applications appeared with invention of controlled/living radical polymerization (CRP)^[2,3] some 20 years ago. From the different CRP techniques known, the nitroxide-mediated controlled/living radical polymerization (NMP)^[4] was the most attractive for Ciba to pursue because the initiators/regulators for NMP are N-alkoxyamines and nitroxides which belong to the Ciba's core competence.

The intensive research work on NMP at Ciba resulted in the development of novel highly efficient alkoxyamines and nitroxides^[5–8] and Ciba was the first company worldwide to realize NMP on industrial scale. Several new products, *e.g.* pigment dispersants, prepared by NMP have already been introduced to the market.^[1] The journey towards industrially feasible NMP was not always foreseeable but also accompanied with unexpected results. One example of such a serendipity observation is the topic of this short article.

Thione to thiol rearrangements are well-known. For example O,S-dialkyl xanthates **1** rearrange thermally^[9,10] or under base catalysis^[11,12] to S,S-dialkyl dithiocarbonates **1a** (Scheme 1). Upon heating, ketoxime O-(S-methyl xanthates) **2** rearrange^[13] to S-imino-S'-methyl-dithiocarbonates **2a** and N,N-dimethylthiocarbamoyl-N'-methylbenzohydroxamates **3** are transformed^[14] already at room tem-

perature slowly into N,N-dimethylcarbamoyl-N'-methylbenzothiohydroxamates **3a**. Synthetically important is the thermal Newman-Kwart rearrangement^[15,16] of O-arylthio carbamates **4** into S-arylthiocarbamates **4a** which enables the transformation of phenols ArOH into the corresponding thiophenols ArSH. Depending on the actual substrate, both ionic^[11,12,16] or free radical^[13,14] mechanisms were postulated for these rearrangements.

During our work on nitroxide-mediated controlled/living radical polymerization (NMP)^[4] we have developed various classes of novel N-alkoxyamines^[5–8] which work as efficient initiators/regulators for NMP. In the same context we observed that the structurally closely related N-acyloxy-2,2,6,6-tetramethylpiperidines do not induce NMP but rather behave as classical free radical initiators.^[17] The principle of NMP is based on the reversible, thermally induced homolysis of the weak (depending on the actual struc-



Scheme 1. Examples of thione-thiol rearrangements.

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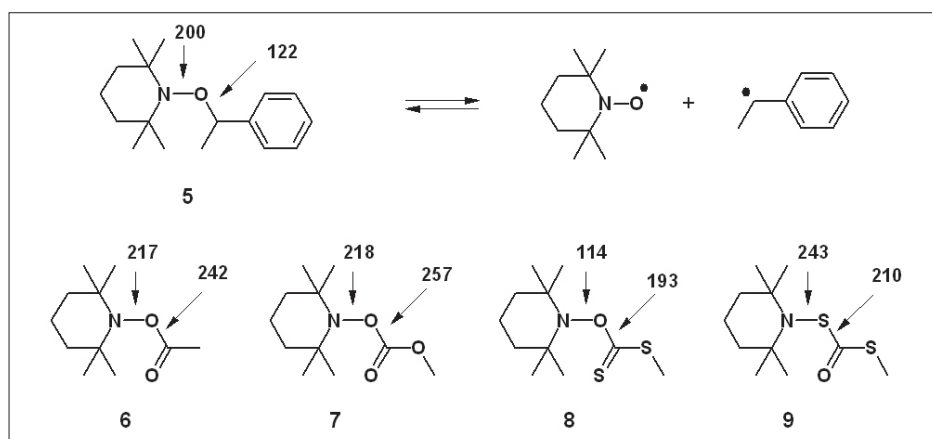
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ture *ca.* 115–135 kJ/mol)^[6,18] NO–C bond of alkoxyamines affording persistent nitroxide radicals and reactive C-centered radicals, as exemplified on 2,2,6,6-tetramethyl-1-(1-phenyl-ethoxy)-piperidine **5** (Scheme 2). Our density functional (DFT) calculations (Scheme 2 and details in the experimental part) of bond dissociation enthalpies (BDE) of the strategic NO–C and N–OC bonds in **5** and in the model compounds, N-acetyloxy-2,2,6,6-tetramethylpiperidine **6** and N-methoxycarbonyloxy-2,2,6,6-tetramethylpiperidine **7** support this observation. Indeed, the calculation predicts for the NO–C bond in the alkoxyamine **5** a BDE of 122 kJ/mol which is in excellent agreement with the experimental value^[18] (119 kJ/mol) and which is less than the BDE of the N–OC bond (200 kJ/mol). The situation is just opposite in the N-acyloxyamines **6** and **7** which suggests that homolysis of these compounds affords two reactive radicals, namely 2,2,6,6-tetramethylpiperidiny and acetyloxy or methoxycarbonyloxy, respectively. These radicals would directly or indirectly initiate the uncontrolled polymerization. The same calculations predict even weaker N–OC bond in the unknown N-methylthiothiocarbonyloxy-2,2,6,6-tetramethylpiperidine **8**. On the other hand the dithiolcarbonate isomer **9** should homolyse along the NS–C bond to afford 2,2,6,6-tetramethylpiperidiny and thionitroxide and methylthiocarbonyl radicals. The low calculated BDE value (114 kJ/mol) of the N–OC bond in **8** led us to speculate that this compound may behave as a free radical initiator working at lower temperature than derivatives of **6** or **7** and hence prompted us to attempt its synthesis. The obvious strategy appeared to be the addition of the anion of N-hydroxy-2,2,6,6-tetramethylpiperidine **10** (Scheme 3) to carbon disulfide followed by methylation. Surprisingly, we have found that addition of the lithium salt of **10** to CS₂ in THF and subsequent treatment with methyl iodide affords the dithiocarbonic acid S-methyl-S'-(2,2,6,6-tetramethylpiperidin-1-yl) ester **9** in 77% yield instead of the expected S-methyl-O-(2,2,6,6-tetramethylpiperidin-1-yl) ester **8**. This unexpected reaction is thus a new example of a thione-thiol rearrangement.

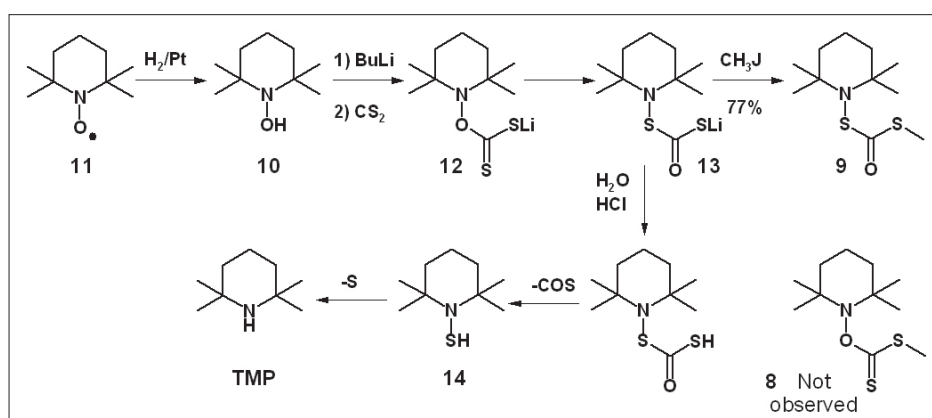
2. Experimental

Solvents and reagents are commercially available and were used as received.

¹H and ¹³C NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz for ¹H and 75.47 MHz for ¹³C). Chemical shifts (δ) are given in ppm downfield from internal Me₄Si standard, J values are in Hz. IR spectra were taken on Nicolet Magna-IR 750 spectrometer in ATR mode,



Scheme 2. Calculated bond dissociation enthalpies in the compounds **5–9** (kJ/mol, 298 K, 1 atm, see introduction).



Scheme 3. Synthesis of the rearranged compound **9**.

MS spectra on Finnigan SSQ 710 apparatus. Elemental analyses were obtained from the Ciba Service Center Elemental Analysis.

The GPC analysis of the polymer was performed on a set of 2 PL-Gel 300 × 7.5 mm (5 μm) mixed C columns + 1 PL-Gel guard column using a Spark Holland Basic Marathon sampler and a Flux RHEOS 4000 pump with inline ERC 1215 α degasser, coupled with ERC 7515A refractometer and ERC7217 UV detector. The column temperature was 40 °C, the detector temperature 30 °C. Tetrahydrofuran was used as eluent (1 ml/min). Polystyrene standards were used for the calibration.

The X-ray structure determination was carried out at Novartis Institutes for Bio-Medical Research, Basel, Switzerland.^[19]

The quantum chemical calculations were conducted with Spartan 06 (Wavefunction, Inc., USA) and Gaussian 03 (Gaussian Inc., USA) suites of programs. The ROB3P86/6-311G(2d,2p)//B3LYP/6-31Gd method, which was used to calculate the bond dissociation enthalpies (including zero point energy and corrections to 298 K, 1 atm), is a slight modification (geometry optimization was performed at B3LYP/6-31Gd instead of B3P86/6-31Gd level) of the well-established procedure^[20] of DiLabio and coworkers. The relative energies

of **8** and **9** were calculated RB3LYP/6-311+G(2d,p)//RB3LYP/6-31G(d) and RMP2-fc/6-311+G(2d,p)//RMP2-fc/6-31G(d) levels. The minima character of all optimized species was confirmed by frequency calculations at the same level, the vibrational frequencies were scaled by the appropriate scaling factors.^[21]

2.1 Dithiocarbonic Acid S-Methyl Ester S-(2,2,6,6-tetramethylpiperidin-1-yl) Ester (**9**)

A solution of 2,2,6,6-tetramethylpiperidine-1-oxyl (**11**, 23.43 g, 0.15 mol, Fluka >96%) in THF (100 ml, dried over molecular sieve) and platinum on charcoal (5% loading) catalyst (450 mg) was hydrogenated at room temperature and 2 bar pressure until the hydrogen uptake ceased (45 min). The mixture was then rapidly filtered into a 1 l three-necked flask filled with argon, the catalyst was washed with THF (150 ml) and the slightly yellow filtrate was cooled to 0 °C. Thereafter, 1.6 M solution of n-butyl lithium in hexane (100 ml, 0.16 mol, Fluka) was added during 45 min and at 0–2 °C and the mixture was stirred for another 30 min at 0 °C under argon. Carbon disulfide (12.56 g, 0.165 mol, Fluka >99%) was then added at 0–2 °C during 20 min. The solution, which

turned from slightly yellow into orange, was stirred at 0 °C for 75 min. Methyl iodide (23.42 g, 0.165 mol, Fluka >99%) was then added during 45 min while keeping the temperature at 0–2 °C and the solution was stirred for additional hour at 0 °C. The resulting orange-yellow solution was then evaporated on a rotary evaporator and water (100 ml) and methyl-*t*-butyl ether (150 ml) was added to the residue. The organic phase was separated, the aqueous layer was diluted with 25% NaCl solution (50 ml) and extracted with methyl-*t*-butyl ether (2 × 50 ml). The combined organic layers were washed with 25% NaCl solution (2 × 40 ml), dried over MgSO₄ and evaporated. The solid, slightly yellow residue (36.4 g) was dissolved in toluene (50 ml) and let crystallize at –20 °C to afford 28.7 g (77.3%) of **9** as almost white, malodorous crystals, mp. 81–83 °C.

Anal. calcd. for C₁₁H₂₁NOS₂ (247.42): C, 53.40; H, 8.56; N, 5.66; S, 25.92. Found: C, 53.46; H, 8.35; N, 5.57; S, 25.94. MS(ESI): *m/z* (%) = 248.2 (100) [M+H]⁺, 142.3 (60). IR, cm^{–1}: 1618 (C=O). ¹H-NMR (300 MHz, CDCl₃): δ = 2.33 (s, 3 H, SCH₃), 1.8–1.4 (m, 6 H, 3 × CH₂), 1.34 (s, 6 H, 2 × CH₃), 1.17 (s, 6 H, 2 × CH₃). ¹³C-NMR (75.38 MHz, CDCl₃): δ = 201.2 (CO), 60.1, 40.5, 32.2, 25.3, 17.3, 12.4. Crystals for X-ray analysis were grown from acetonitrile.

2.2 Bulk Polymerization of *n*-Butylacrylate with (**9**)

A magnetically stirred solution of **9** (0.247 g, 1 mmol) in *n*-butyl acrylate (12.82 g, 10 mmol) in a 50 ml round flask was degassed by three vacuum/argon cycles and was then heated at 140 °C for 90 min to afford colorless, very viscous polymer. Integration of the ¹H-NMR (CDCl₃) signals of the OCH₂ groups of the unreacted monomer (4.16 ppm) and polymer (4.0 ppm) indicated 92% conversion. GPC: M_n = 67291, M_w = 580861, M_w/M_n = 8.6.

3. Results and Discussion

Reports on reactions of *N,N*-dialkyl hydroxylamines with carbon disulfide are very scarce. Haase and Woffenstein observed deoxygenation of diethyl- or dibenzyl hydroxylamine upon heating with CS₂, however the structure of the products was not conclusively elucidated.^[22] Recently, preparation of stable *O*-dialkylamino xanthates starting from diethyl- or benzylphenyl hydroxylamine and their use as agents for controlled/living radical polymerization was described^[23] in the patent literature, however, no analytical data were provided for these compounds.

Our attempted synthesis of **8** is depicted in Scheme 3. Catalytic hydrogenation of 2,2,6,6-tetramethylpiperidine-*N*-oxyl

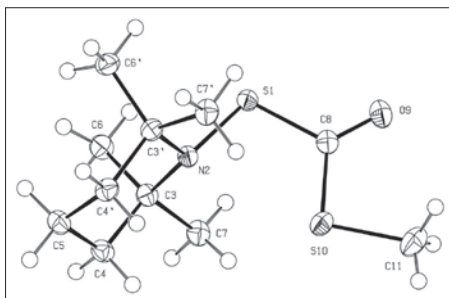


Fig. 1. X-ray structure of **9**.

11 afforded in quantitative yield the hydroxylamine **10**. Deprotonation of **10** with *n*-butyllithium in THF followed by subsequent addition of CS₂ and methyl iodide yielded the rearranged compound **9** in 77% isolated yield instead of the expected isomer **8**. The TLC of the crude reaction mixture before isolation showed that **9** is the only product formed. The structure of **9** has been confirmed by elemental analysis, mass spectrometry, ¹H and ¹³C-NMR and IR-spectroscopy. Most striking is the presence of the strong >C=O group absorption at 1618 cm^{–1}, the >C=S group of the isomer **8** would not absorb in this region. Moreover, the ¹³C-resonance at 201.2 ppm is compatible with the structure **9** but not **8** whose >C=S signal is expected between 230–240 ppm. The ultimate proof of the structure **9** was obtained by X-ray analysis of single crystals grown from acetonitrile (Fig. 1).

The detailed mechanism of this novel rearrangement is not clear yet. However, the observation that addition of one equivalent of aqueous HCl instead of methyl iodide affords 2,2,6,6-tetramethylpiperidine (TMP) and elemental sulfur instead of **10** and CS₂ suggests that it is the Li-xanthogenate **12** which rearranges into the Li-dithiocarbonate **13**. The methylation of **13** then affords **9**. The formation of TMP and sulfur *via* the mercapto amine **14** can be plausibly explained (Scheme 3). Decomposition of *N*-mercapto amines to amines and sulfur is known.^[24]

We suppose that the main contribution to the thermodynamic driving force of the novel rearrangement originates from the transformation of a relatively weak C=S bond into a strong C=O bond. Indeed, calculations with DFT and Moeller-Plesset theory (see Experimental) lead to the same result indicating that the ground state energy (298 K, 1 atm) of **9** is 132.9 kJ/mol resp. 132.5 kJ/mol lower than that of **8**.

The compound **9** is a protected thionitroxide, the novel rearrangement thus opens a new access to thionitroxide derivatives.^[25] Bricklebank and Pryke reported^[26] that radical polymerization of styrene in the presence of 2,2,6,6-tetramethylpiperidyl-1-thiyl affords polystyrene with

high polydispersity (M_w/M_n = 1.9–4) and is therefore not controlled/living.

We were able to polymerize bulk *n*-butylacrylate with 1 mol% of **9** at 140 °C. However, the corresponding polymer, obtained in 92% yield, was highly polydisperse (M_w/M_n = 8.6) which indicates an uncontrolled polymerization in this case too.

4. Conclusions

We have reported a novel thione-thiol rearrangement of dithiocarbonic acid *O*-(2,2,6,6-tetramethylpiperidin-1-yl) ester affording the first example of the hitherto unknown thionitroxide derivatives. The new compound **9** is a radical initiator for the thermal polymerization *n*-butylacrylate even though the polymerization is not controlled/living.

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