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Thermal Elimination of Diethyldithiocarbamates and Application in the Synthesis of (±)-Ferrugine

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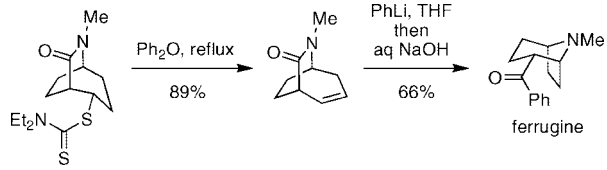
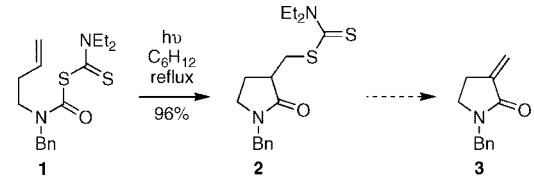


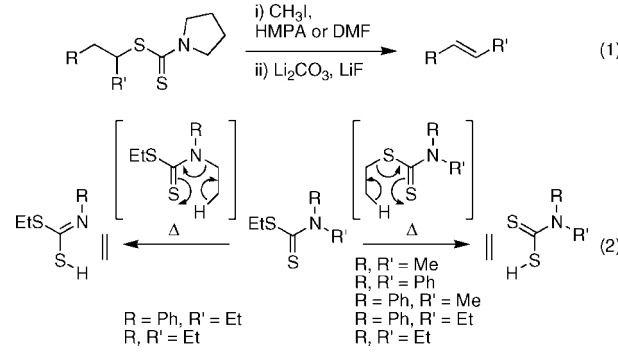
Dithiocarbamate-substituted lactams, prepared through group-transfer cyclization reactions of carbamoyl radicals, undergo a Chugaev-like thermal elimination of the dithiocarbamate group in refluxing diphenyl ether to form α,β- and/or β,γ-unsaturated amides, depending on the structure of the starting material. This reaction sequence was used to prepare an unsaturated [3.2.2] bridged bicyclic amide, which was converted in a one-pot procedure to the 8-azabicyclo[3.2.1]octane ring system of the tropane alkaloid ferrugine by treatment with phenyllithium followed by aqueous sodium hydroxide.

Nonreductive, atom- or group-transfer radical addition reactions offer the advantage of greater product functionalization compared with processes based on hydrogen atom abstraction (e.g., from Bu_3SnH).[1] We have recently reported a new method for the generation and cyclization of carbamoyl radicals from diethyldithiocarbamate precursors (Scheme 1).[2] Group transfer of the dithiocarbamate is key to maintaining the radical chain process, and also offers a useful functionality within the product for further manipulation. In order to extend the synthetic utility of this methodology, we have investigated further transformations of the dithiocarbamate group. In the course of a synthesis of the alkaloid aphanorphine, we have described a novel photomediated dithiocarbamate−TEMPO exchange reaction that formally achieves the transformation of a carbon−sulfur bond into a carbon−oxygen bond.[3] In this note, we report our studies into the elimination of the diethyldithiocarbamate group to form

SCHEME 1. Dithiocarbamate Group Transfer Carbamoyl Radical Cyclization and Proposed Elimination



SCHEME 2. Elimination of Dithiocarbamates under Basic and Thermal Conditions



both α,β- and β,γ-unsaturated amides, depending on the structure of the lactam.

A limited number of reports have described the elimination of the dithiocarbamate group to give alkenes. Hayashi reported that *S*-methylation of the nucleophilic thiocarbonyl group in pyrrolidine dithiocarbamates, followed by base-mediated elimination of the resulting sulfonium salt, gave good to excellent yields of conjugated alkenes (Scheme 2, eq 1; R, R′ = aryl, alkenyl).[4]

The thermal elimination of dithiocarbamates was first investigated by Chande.[5] Heating *S*-ethyl *N*-disubstituted dithiocarbamates in the solid state (250−285 °C) gave rise to ethylene, carbon disulfide, and a secondary amine, consistent with a Chugaev-like pyrolytic elimination via an E^i mechanism followed by further decomposition of the dithiocarbamic acid thus formed (Scheme 2, eq 2). When one or both of the N-substituents was ethyl, additional products were observed resulting from competitive elimination of ethylene from the ethyl group on nitrogen as well as sulfur. Thermal dithiocarbamate elimination has been applied to the synthesis of highly conjugated polymers by heating polymeric benzylic diethyldithiocarbamates either as thin films or in solution (1,2-dichlorobenzene 175 °C).[6] Thermal elimination from 1,2-bis(dithiocarbamato)-1,2-dialkoxyalkanes to form 1-dithiocarbamato-1,2-dialkoxyalkenes would

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(1) (a) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001; Vol. 1, pp 72−89. (b) Zard, S. Z. *Radicals Reactions in Organic Synthesis*; Oxford University Press: New York, 2003; Chapter 6.
(2) Grainger, R. S.; Innocenti, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3445.
(3) Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377.
(4) (a) Hayashi, T.; Sakurai, A.; Osihi, T. *Chem. Lett.* **1977**, 1483. (b) Hayashi, T.; Hori, I.; Oishi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2909. (c) Hayashi, T.; Yanagida, M.; Matsuda, Y.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2665. (d) Hayashi, T.; Oishi, T. *Chem. Lett.* **1985**, 413. (e) Hayashi, T.; Sasaoka, K.; Oishi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1362.
(5) Chande, M. S. *J. Indian Chem. Soc.* **1979**, *56*, 386.
(6) (a) Padmanaban, G.; Nagesh, K.; Ramakrishnan, S. *J. Polym. Sci. Part A: Polym. Chem.* **2003**, *41*, 3929. (b) Henckens, A.; Colladet, K.; Fourier, S.; Cleij, T. J.; Lutsen, L.; Gelan, J.; Vanderzande, D. *Macromolecules* **2005**, *38*, 19. (c) Henckens, A.; Duyssens, I.; Lutsen, L.; Vanderzande, D.; Cleij, T. J. *Polymer* **2006**, *47*, 123. (d) Palmaerts, A.; van Haren, M.; Lutsen, L.; Cleij, T. J.; Vanderzande, D. *Macromolecules* **2006**, *39*, 2438.

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appear to be relatively facile in solution (DMSO or toluene, 110 °C)[7a,c−e] and has also been reported to occur in the solid state (190 °C, 0.2 Torr).[7b] Whether this variant occurs via a concerted elimination or a stepwise process has not been determined. Recently, 5,6-dihydropyridin-2(1*H*)-one was prepared by heating 2-oxopiperidin-3-yl dimethyldithiocarbamate to 260 °C at 1 Torr.[8]

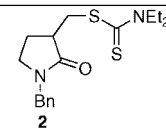
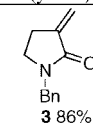
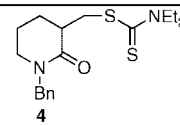
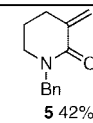
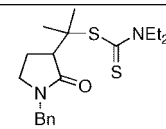
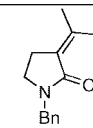
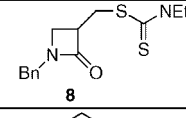
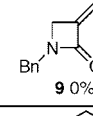
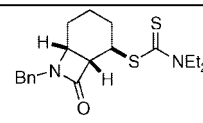
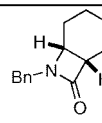
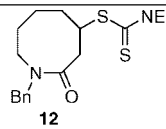
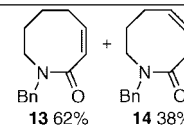
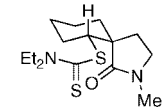
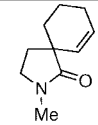
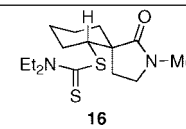
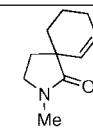
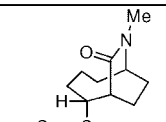
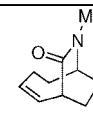
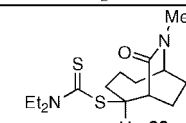
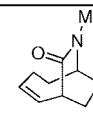
We initiated our investigations by attempting a base-mediated elimination of readily prepared diethyldithiocarbamate **2**.[2] Treatment of **2** with DBU in chloroform or toluene, conditions used for the β-elimination of xanthates to form enoates at room temperature,[9] failed to provide any of the expected alkene **3**, even after refluxing for extended periods. In order to increase the nucleofugacity of the dithiocarbamate group, we next applied the Hayashi *S*-methylation−elimination conditions, in either DMPU or DMF as solvent. However, even after prolonged reaction times and heating, only traces of alkene **3** were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Hayashi noted that the nature of the *N*-alkyl moiety in the dithiocarbamate group is important for a successful reaction. *N*,*N*-Dimethyl- and *N*,*N*-diisopropyldithiocarbamates did not give good yields, whereas 1-pyrrolidinecarbodithioates gave fair to excellent yields.

We therefore turned our attention to thermal elimination. A survey of common laboratory solvents of increasing boiling point (chlorobenzene, 1,3-dichlorobenzene, DMSO) demonstrated that dithiocarbamate **2** was thermally stable to high temperatures, with only a trace amount of alkene **3** being observed after 10 h of reflux in 1,2,4-trichlorobenzene (bp 214 °C). However, in refluxing diphenyl ether (bp 259 °C), a smooth, high-yielding transformation to alkene **3** occurred over the course of a few hours. The alkene was easily purified by subjecting the reaction mixture to direct column chromatography. The nonpolar diphenyl ether is rapidly eluted, followed by alkene **3** upon increasing solvent polarity.

To probe the generality of this method, a range of diethyl dithiocarbamates, prepared through group transfer cyclization of carbamoyl radicals,[2,10] was subjected to thermal elimination in refluxing diphenyl ether. The results are presented in Table 1.

Despite the high temperatures involved, the products of the reaction proved to be thermally robust, and the reaction was successful in all but one case evaluated (entry 4). In this latter case, the simple β-lactam **9** containing an exocyclic methylene group did not survive the reaction conditions (if formed); however, β-lactam **11** was produced in good yield (entry 5). Formation of a conjugated alkene is not a prerequisite for a successful outcome of the reaction, and both exocyclic (entries 1−3) and endocyclic (entries 5−10) alkenes can be formed. Two regiochemical outcomes are possible in the thermal elimination of dithiocarbamates **6**, **10**, and **12**. Conjugated tetrasubstituted alkene **7** is the exclusive product from elimination of **6** (entry 3), and high regioselectivity is also observed in the formation of β,γ-unsaturated alkene **11** from β-lactam **10** (entry 5). In this case, elimination to form the α,β-unsaturated amide is presumably disfavored due to developing strain. In the case of 8-ring lactam **12**, a mixture of double bond isomers **13** and **14** is obtained (entry 6). Independently resubjecting both **13** and **14** to refluxing diphenyl ether for 4 h did not result in

TABLE 1. Thermal Elimination of Diethyldithiocarbamates[a]

Entry	Dithiocarbamate	Time (h)	Alkene (yield[b])
1	 **2**	2	 **3** 86%
2	 **4**	5	 **5** 42%
3	 **6**	1	 **7** 84%
4	 **8**	-	 **9** 0%
5	 **10**	2	 **11** 79%
6	 **12**	4.25	 **13** 62% **14** 38%
7	 **15**	4	 **17** 89%
8	 **16**	11	 **17** 90%
9	 **19**	2	 **21** 80%
10	 **20**	2	 **21** 81%

[a] Conditions: Ph_2O, 0.05−0.1 M, reflux. [b] Isolated yield after column chromatography.

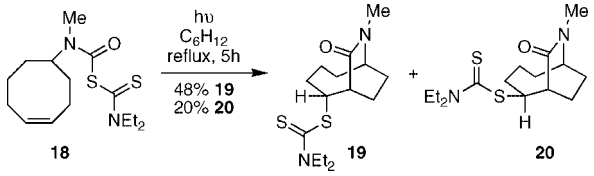
(7) (a) Suzuki, T.; Yamochi, H.; Srdanov, G.; Hinkelmann, K.; Wudl, F. *J. Am. Chem. Soc.* **1989**, *111*, 3108. (b) Hartke, K.; Lindenblatt, T. *Synthesis* **1990**, 281. (c) Papavassiliou, G. C.; Kakoussis, V. C.; Lagouvardos, D. J.; Mousdis, G. A. *Mol. Cryst. Liq. Cryst.* **1990**, *181*, 171. (d) Misaki, Y.; Nishikawa, H.; Nomura, K.; Yamabe, T.; Yamochi, H.; Saito, G.; Sato, T.; Shiro, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1410. (e) Iyoda, M.; Kuwatani, Y.; Ogura, E.; Hara, K.; Suzuki, H.; Takano, T.; Takeda, K.; Takano, J.-i.; Ugawa, K.; Yoshida, M.; Matsuyama, H.; Nishikawa, H.; Ikemoto, I.; Kato, T.; Yoneyama, N.; Nishijo, J.-i.; Miyazaki, A.; Enoki, T. *Heterocycles* **2001**, *54*, 833.

(8) Simón, L.; Muñiz, F. M.; Sáez, S.; Raposo, C.; Sanz, F.; Morán, J. R. *Helv. Chim. Acta* **2005**, *88*, 1682.

(9) Forbes, J. E.; Saicic, R. N.; Zard, S. Z. *Tetrahedron* **1999**, *55*, 3791.

(10) Dithiocarbamates **2**, **4**, **8**, **10**, **12**, **15**, and **16** have been previously reported.[2] The preparation of **6**, **18**, **19** and **20** is described in Supporting Information.

SCHEME 3



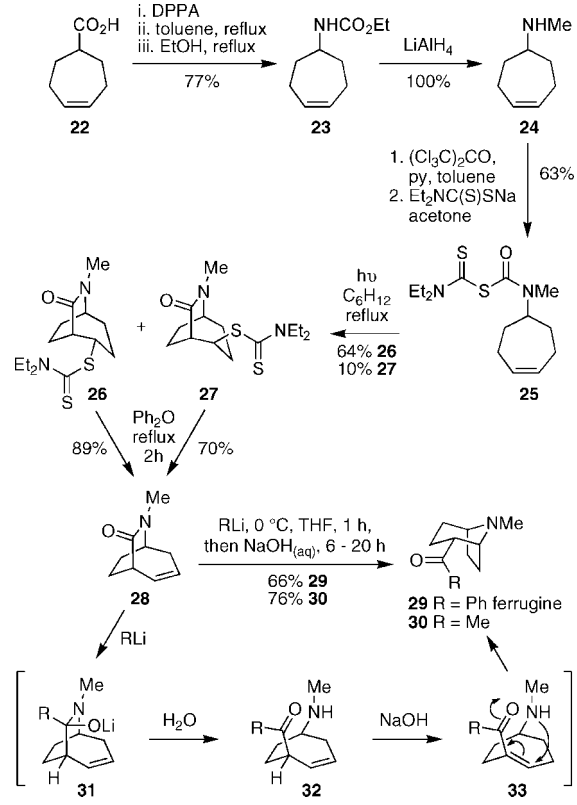
any interconversion. Similar yields of spirocyclic alkene **17** are obtained starting from the two diastereomeric diethyldithiocarbamates **15** and **16** (entries 7 and 8). Similarly, dithiocarbamates **19** and **20**, formed from a regioselective 6-*exo-trig* radical cyclization followed by a moderately diastereoselective dithiocarbamate group transfer (Scheme 3), are eliminated in similar yields in a stereoconvergent synthesis of alkene **21** (entries 9 and 10).[11,12]

Based on the Chugaev-like E^i mechanism proposed by Chande, formation of diethylaminodithiocarbamic acid would be one of the expected byproducts from the thermal elimination of the diethyldithiocarbamates used in this study. At high temperature diethylaminodithiocarbamic acid would break down to diethylamine and CS_2, whose volatility would result in both byproducts being lost from solution under the reaction conditions. The absence of any products derived from conjugate addition of diethylamine to α,β-unsaturated enamides **3**, **5**, **7**, or **13** is perhaps notable in this regard. In contrast to the work of Chande, we did not observe products arising from competitive elimination into the ethyl group of the amine.

Application of this methodology in a synthesis of ferrugine, a tropane alkaloid isolated from *Darlingia ferruginea* J. F. Bailey,[13] is shown in Scheme 4. Treatment of the known carboxylic acid **22**[14] with DPPA gave the corresponding acyl azide, which after Curtius rearrangement and trapping of the resulting isocyanate with ethanol gave the carbamate **23**. Reduction of **23** using $LiAlH_4$ gave the somewhat volatile methylamine **24**, which was treated first with triphosgene and pyridine to give a carbamoyl chloride and then with sodium diethyldithiocarbamate to give the radical cyclization precursor **25**. Initiation of the radical chain process by irradiation of a solution of **25** in cyclohexane with a 500 W halogen lamp gave rise to a mixture of diastereomeric diethyldithiocarbamates **26** and **27** through a formal 6-*exo-trig* cyclization. The stereochemistry of the major diastereomer **26** was confirmed by X-ray crystallography.[12] Both stereoisomers converged to a single alkene **28** upon thermal elimination of the dithiocarbamate group.[15]

Treatment of 6-azabicyclo[3.2.2]non-2-ene **28** with phenyllithium for 1 h at 0 °C, followed by quenching with dilute sodium hydroxide solution and stirring the resulting biphasic mixture at room temperature for 6 h, gave directly the tropane alkaloid ferrugine **29** in 66% isolated yield. The relative

SCHEME 4. Total Synthesis of Ferrugine



stereochemistry in **29** was confirmed by X-ray crystallography of the corresponding perchlorate salt.[12] Similarly, reaction of **28** with MeLi gave the tropane alkaloid derivative as a 6:1 mixture of diastereomers from which the major isomer **30** could be isolated in 76% yield. This one-pot, multistep transformation is envisaged to occur through nucleophilic attack to give **31**, which upon workup liberates the aminoketone **32**, presumably in equilibrium with the corresponding hemiaminal (we did not observe the formation of any tertiary alcohol resulting from over addition to an intermediate ketone despite the use of excess organolithium). Under the influence of base, the double bond in **32** enters into conjugation with the ketone to give **33**, which undergoes intramolecular conjugate addition to give the tropane alkaloid skeleton. The resulting stereocenter was found to be under thermodynamic control, with **30** epimerizing to the same 6:1 mixture upon treatment with aqueous NaOH.

In conclusion, unsaturated lactams are produced in good yield through the thermal elimination of a diethyldithiocarbamate group in refluxing diphenyl ether. This operationally simple reaction benefits from the volatile nature of the side products, which renders workup and purification straightforward. This methodology extends the synthetic utility of the carbamoyl radical cyclization−dithiocarbamate group transfer reaction, as demonstrated in the synthesis of the tropane alkaloid ferrugine.

Experimental Section

Representative Procedure for the Thermal Elimination of Diethyldithiocarbamates.

1-Benzyl-3-methylene-pyrrolidin-2-one 3. A solution of dithiocarbamate **2**[2] (820 mg, 2.44 mmol) in diphenyl ether (24 mL) was heated at reflux for a period of 2 h, under 1 atm of argon. The reaction mixture was purified by column chromatography (2:1−1:1 petroleum ether/diethyl ether), yielding the exocyclic alkene **3** (394

(11) The regio-and stereoselectivity of the cyclization of **18** was determined by X-ray analysis of alkene **21** and dithiocarbamate **20**, respectively.

(12) File in cif format is available in Supporting Information. CCDC 682056 and CCDC 695282−695284 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

(13) (a) Bick, I. R. C.; Gillard, J. W.; Woodruff, M. *Chem. Ind. (London)* **1975**, 794. (b) Bick, I. R. C.; Gillard, J. W.; Leow, H.-M. *Aust. J. Chem.* **1979**, *32*, 2537.

(14) Marquardt, D. J.; Newcomb, M. *Synth. Commun.* **1988**, *18*, 1193.

(15) Alkene **28** can also be prepared directly from **25** through tandem radical cyclization−thermal elimination, although in lower overall yield compared to the two-step process. Irradiation of **25** in refluxing diphenyl ether gave **28** in 37% isolated yield.

mg, 86%) as a yellow oil. Analytical data agree with that reported in the literature.[16] ν_{max} (neat)/cm^{-1} 3031, 2239, 1684, 1655, 1448; δ_H (360 MHz; $CDCl_3$) 2.71−2.77 (2H, m), 3.25 (2H, t, $J = 6.7$), 4.56 (2H, s), 5.36−5.37 (1H, m), 6.02−6.06 (1H, m), 7.25−7.37 (5H, m); δ_C (90 MHz; $CDCl_3$) 23.9 (CH_2), 42.4 (CH_2), 47.2 (CH_2), 115.6 (CH_2), 127.6 (CH), 128.2 (CH), 128.6 (CH), 136.2 (C), 139.5 (C), 167.8 (C); *m*/*z* (EI) 187 ($M^{+\bullet}$; 100), 158 (12), 130 (7), 110 (11), 104 (8), 96 (24), 91 (72), 83 (14), 77 (6); HRMS (EI) calcd for $C_{12}H_{13}N_1O_1Na$ 210.0890, found 210.0885.

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Supporting Information Available: Experimental procedures, analytic data and copies of ^{1}H and ^{13}C NMR for all new compounds, and X-ray crystal data of **20**, **21**, **26** and perchlorate salt of **29** as cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585.