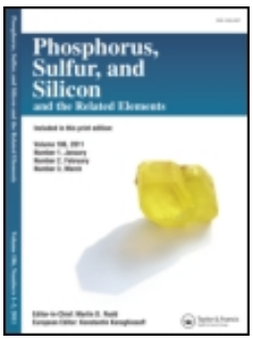

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LITHIUM DIISOPROPYLAMIDE (LDA) AS AN EFFICIENT REDUCING AGENT FOR THIOKETONES—MECHANISTIC CONSIDERATION

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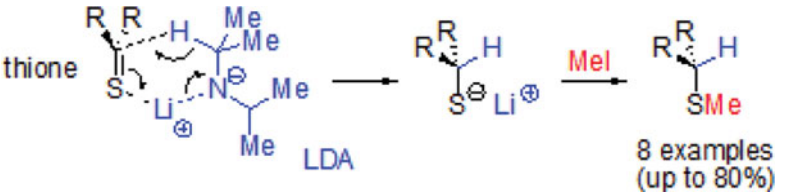
GRAPHICAL ABSTRACT



Abstract *Treatment of thiocarbonyl compounds with excess of lithium diisopropylamide (LDA) leads to corresponding thiols or sulfides depending on the work-up procedure. The mechanistic scenario for this unusual reduction pathway is discussed.*

Keywords Thioketones; LDA; hydride transfer; sulfides; reaction mechanisms

INTRODUCTION

Thioketones belong to the class of reactive dipolarophiles (so-called superdipolarophiles) widely applied for the synthesis of numerous *S*-heterocylic systems.[1] However, their behavior toward lithiated agents is by far less well known. As a part of our ongoing project focused on the exploration of thioketones in organic, materials, coordination, and biometallo-organic chemistry,[2] a series of model compounds of type **1** were recently shown to be suitable reaction partners in reactions with *C*-nucleophiles. For example, treatment of adamantanethione (**1a**) with lithiated methylphosphonate followed by methyl iodide or with methoxyallene anion provided the corresponding products, i.e., the phosphonylated sulfide **2**[3] and vinylthiirane derivative **3**,[4] respectively, as a result of exclusive *carbophilic* attack onto the C═S group (Scheme 1).

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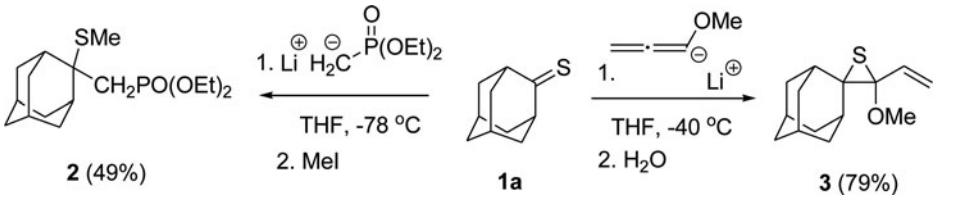
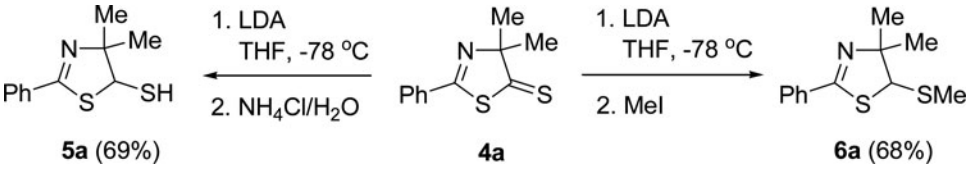


Scheme 1 Reactions of adamantanethione (**1a**) with lithiated *C*-nucleophiles.

Within the studies on [3 + 2]-cycloadditions of thioketones with azomethine ylides, 1,3-thiazole-5(4*H*)-thione **4a** was selected as a model compound.[5] Unexpectedly, the treatment of a mixture of **4a** and trimethylamine oxide, used as an anticipated source of the parent azomethine ylide,[6] with lithium diisopropylamide (LDA) at 0°C provided only the reduction product **5a**. Further experiments with **4a** confirmed the unusual potential of LDA for the reduction of C=S groups. Thus, depending on the work-up procedure, the corresponding thiol **5a** or methylsulfide **6a** was obtained in high yields[7] (Scheme 2).



Scheme 2 Reduction of 1,3-thiazole-5(4*H*)-thione **4a** with LDA.

RESULTS AND DISCUSSION

Following the protocol established for compound **4a**, a spirocyclic 1,3-thiazole-5(4*H*)-thione of type **4** and a series of thioketones **1** were smoothly reduced with excess of LDA to give respective thiolates, which after trapping with methyl iodide as an electrophile provided the expected products **6b** and **7a**–**f**, respectively, in high yields (Figure 1). Analytically pure samples of products were obtained after chromatographic purification in 40–80% yields. Hence, as shown in Figure 1, dithioacetals **6a**–**b** as well as cycloaliphatic (**7a**–**b**) and aromatic (**7c**–**f**) sulfides, including unique diferrocenyl (**7e**) and hetaryl (**7f**) derivatives, are available by the presented method, although the yields in the latter cases are rather low.[7]

Although lithium amides are known in the first line as strong bases, often used for the deprotonation of CH-acidic compounds, reducing properties of LDA and its analogs have been also reported.[8] For example, LDA-induced conversion of nitroarenes to the corresponding aromatic amines and azoxyarenes via a single electron transfer (SET) mechanism was described.[8a] An analogous reaction pathway was postulated for the observed formation of sulfides from 2,2-diaryl-1,3-dithiolanes via the in situ generated aromatic thioketones.[8b] On the other hand, treatment of 4-fluorotoluene with LDA in diethyl ether gave, among other products, a mixture of *meta*- and *para*-ethyl(2-tolylethyl)amine.[9a] A reaction mechanism via hydride transfer from $LiNEt_2$ to the intermediate aryne, and subsequent addition of aryl anion to the formed imine, was proposed. Furthermore, the reduction of benzophenone with $LiNEt_2$ was interpreted as a hydride-transfer reaction via a six-membered transition state.[9b]

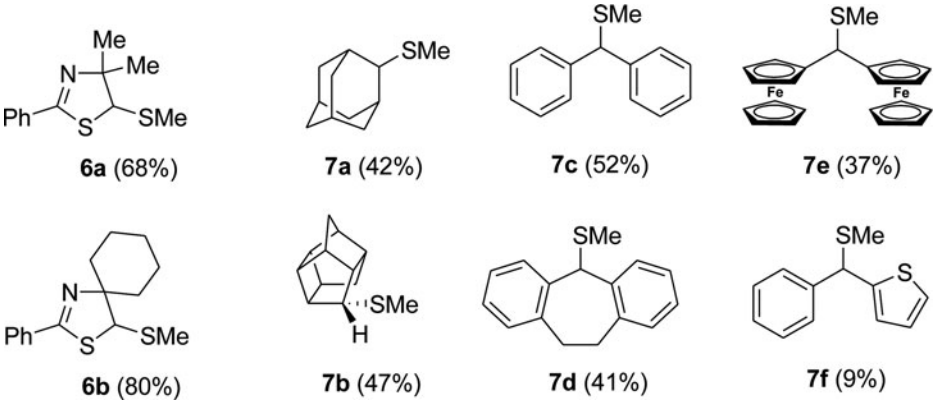
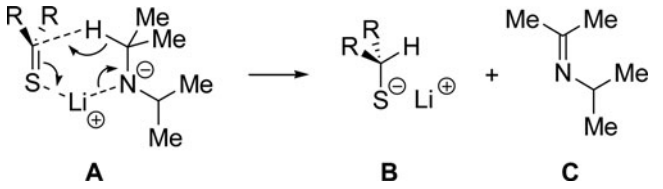


Figure 1 Products **6** and **7** prepared by the reduction of respective thiocarbonyl substrates.

A strong evidence for this reaction mechanism is the enantioselective reduction of ketones with enantiomerically pure lithium alkyl phenyl amides[9c] and lithium dialkylamides.[9d] This pathway resembles that of reactions of Grignard reagents with sterically demanding carbonyl compounds as well as the Meerwein–Schmidt–Ponndorf–Verley reductions of ketones.[10]

Based on the above-discussed reports, we suggest that LDA in the reaction with non-enolizable thioketones acts as a hydride donor. Hydride transfer via the six-membered transition state **A** then leads to thiolate **B**, which can be protonated or trapped with appropriate electrophiles. The respective imine **C** is formed as a side-product (Scheme 3). A small amount of the imine **C** was identified in the ^{1}H-NMR spectra of crude mixtures obtained with both adamantanethione (**1a**) and thiobenzophenone (**1c**); a characteristic septet attributed to the C*H*Me$_2$ group was found at 3.77 ppm.[11] In addition, no incorporation of a deuterium atom was observed when the reaction of LDA with **4a** was performed in THF-d_8.[7] However, the competitive SET mechanism, especially in the case of hetaryl-substituted thioketone **1f**, can not be ruled out.



Scheme 3 Postulated transition state (**A**), and hydride shift leading to thiolate (**B**).

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REFERENCES

1. (a) Fišera, L.; Huisgen, R.; Kalwinsch, I.; Langhals, E.; Li, X.; Mlostoń, G.; Polborn, K.; Rapp, J.; Sicking, W.; Sustmann, R. *Pure Appl. Chem.* **1996,** 68, 789–798; (b) Mlostoń, G.; Heimgartner, H. In: A. Padwa and W. H. Pearson (Eds.), *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: New York, NY, 2002; pp. 315–360; (c) Mlostoń, G.; Heimgartner, H. In: O. A. Attanasi and D. Spinelli (Eds.), *Targets in Heterocyclic Systems*, Vol. 10; Italian Society of Chemistry: Rome, **2006**; pp. 266–300.
2. (a) Mlostoń, G.; Urbaniak, K.; Gębicki, K.; Grzelak, P.; Heimgartner, H. *Heteroatom Chem.* **2014,** 25, 548–555; (b) Mlostoń, G.; Urbaniak, K.; Szychowska, A.; Linden, A.; Heimgartner, H. *Heterocycles* **2015,** 90, 529–539; (c) Mlostoń, G.; Pipiak, P.; Heimgartner, H. *Helv. Chim. Acta* **2015,** 98, 462–473.
3. Mlostoń, G.; Obijalska, E.; Urbaniak, K.; Heimgartner, H. *Heteroatom Chem.* **2008,** 19, 182–187.
4. Jasiński, M.; Mlostoń, G.; Stolarski, M.; Costa, W.; Domínguez, M.; Reissig, H.-U. *Chem. Asian J.* **2014,** 9, 2641–2648.
5. (a) Gebert, A.; Linden, A.; Mlostoń, G.; Heimgartner, H. *Heterocycles* **2002,** 56, 393–402; (b) Gebert, A.; Mlostoń, G.; Linden, A.; Heimgartner, H. *Pol. J. Chem.* **2003,** 77, 157–167; (c) Gebert, A.; Linden, A.; Mlostoń, G.; Heimgartner, H. *Pol. J. Chem.* **2003,** 77, 867–879.
6. (a) Beugelmans, R.; Negron, G.; Roussi, G. *J. Chem. Soc. Chem. Commun.* **1983,** 31–32; (b) Beugelmans, R.; Chastanet, J.; Roussi, G. *Heterocycles* **1987,** 26, 3197–3202; (c) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1988,** 53, 3808–3812.
7. Gebert, A.; Jasiński, M.; Mlostoń, G.; Heimgartner, H. *Helv. Chim. Acta* **2014,** 97, 931–938.
8. (a) Wang, A.; Biehl, E. *Arkivoc* **2002,** (*i*), 71–75; (b) Ikehira, H.; Tanimoto, S.; Oida, T.; Okano, M. *J. Org. Chem.* **1983,** 48, 1120–1122; (c) Ashby, E. C.; Deshponde, A. K.; Patil, G. S. *J. Org. Chem.* **1995,** 60, 663–672; (d) De Kimpe, N.; Yao, Z. P.; Schamp, N. *Tetrahedron Lett.* **1986,** 27, 1707–1710; (e) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1984,** 106, 8276–8282; (f) Newkome, G. R.; Hager, D. C. *J. Org. Chem.* **1982,** 47, 599–601; (g) Shen, C. C.; Ainsworth, C. *Tetrahedron Lett.* **1979,** 20, 89–92. (h) For a review see: Majewski, M.; Cleave, D. M. *J. Organomet. Chem.* **1994,** 470, 1–16.
9. (a) Wittig, G.; Rentzea, C. N.; Rentzea, M. *Liebigs Ann. Chem.* **1971,** 744, 8–14; (b) Wittig, G.; Schmidt, H.-J.; Renner, H. *Chem. Ber.* **1962,** 95, 2377–2383; (c) Wittig, G.; Thiele, U. *Liebigs Ann. Chem.* **1969,** 726, 1–12; (d) Takeda, K.; Ohnishi, Y.; Koizumi, T. *Org. Lett.* **1999,** 1, 237–239.
10. (a) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1989,** 2, 205–213; (b) Campbell, E. J.; Zhou, H.; Nguyen, S.-B. T. *Angew. Chem. (Int. Ed.)* **2002,** 41, 1020-1022; *Angew. Chem.* **2002**, *114*, 1062–1064.
11. Bunnelle, W. H.; Singam, P. R.; Narayanan, B. A.; Bradshaw, C. W.; Liou, J. S. *Synthesis* **1997,** 439–442.