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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 LDA leads to the 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-heterocyclic systems.1 However, their behavior towards 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 biometalloorganic chemistry,2 a series of model compounds of type 1 was 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 23 and vinylthiirane derivative 3,4 respectively, as the result of exclusive carbophilic attack onto the C=S group (Scheme 1).
Scheme 1 Reactions of adamantantelline (1a) with lithiated C-nucleophiles.

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

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

RESULTS AND DISCUSSION

Following the protocol established for compound 4a, a spirocyclic 1,3-thiazole-5(4H)-thione of type 4 and a series of thioketones 1 were smoothly reduced with excess of LDA to give the respective thiolates, which after trapping with methyl iodide as the 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, dithiaoacetals 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, though the yields in the latter cases are rather low.
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 also been reported. For example, LDA-induced conversion of nitroarenes to the corresponding aromatic amines and azoxyarenes via a single electron transfer (SET) mechanism was described. 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. 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-tolyethyl)amine. A reaction mechanism via hydride transfer from LiNEt$_2$ to the intermediate aryne and subsequent addition of the 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. A strong evidence for this reaction mechanism are enantioselective reductions of ketones with enantiomerically pure lithium alkyl phenyl amides and lithium dialkylamides. This pathway resembles that of reactions of Grignard reagents with sterically demanding carbonyl compounds as well as Meerwein-Schmidt-Ponndorf-Verley reductions of ketones.

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

Based on the reports discussed above we suggest, that LDA in the reaction with non-enolizable thioketones acts as a hydride donor. Hydride transfer via the 6-membered
transition state A leads then to thiolate B, which can be protonated or trapped with appropriate electrophiles. The respective imine C is formed as a side-product (Scheme 3). However, the competitive SET mechanism, especially in the case of hetaryl substituted thioketone If, can’t be ruled out.

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[11] A small amount of the imine C was identified in the $^1$H NMR spectra of crude mixtures obtained with both adamantanthione (1a) and thiobenzophenone (1c); a characteristic septet attributed to the CHMe$_2$ group was found at 3.77 ppm.$^{12}$ In addition, no incorporation of a deuterium atom was observed, when the reaction of LDA with 4a was performed in THF-d$_8$.