Highly Stereoselective Access to Sulfur Derivatives Starting from Zinc Organometallics

Arkady Krasovskiy, Andrey Gavryushin, Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 München, Germany Fax +49(89)218077680; E-mail: Paul.Knochel@cup.uni-muenchen.de Received 23 December 2005

Abstract: A number of organozinc reagents was found to react with tetramethylthiuram disulfide [(Me₂NCS₂)₂] giving dithiocarbamates with complete retention of configuration in the case of chiral compounds.

Key words: organozinc reagents, tetramethylthiuram disulfide, sulfur, chirality

Many aromatic and aliphatic thio derivatives have biological activities and their synthesis has recently attracted a lot of attention.^{1,2} Especially, a number of new copperand palladium-catalyzed aryl–sulfur bond formation reactions have been described.² Recently, we reported a general procedure for the thiolation of magnesium organometallics using tetramethylthiuram disulfide (1),³ a cheap and commercially available thiolation reagent.⁴

The reaction between **1** (TMTD) and Grignard reagents (complexed with LiCl)⁵ provides aryl- and heteroaryl-N,N-dimethyldithiocarbamates in good to excellent yields. These thio derivatives can be easily converted to various sulfur-containing products by simple transformations.³ Encouraged by these results and taking in account the easy accessibility of chiral organozinc compounds, we have investigated the reaction between **1** (TMTD) and different mono- (**2**) and diorganozinc (**3**) compounds (Scheme 1 and Table 1).



Scheme 1

Thus, the reaction of phenylzinc chloride (2a) with a CH_2Cl_2 solution of TMTD (1) furnishes after two hours the dithiocarbamate 4a in 88% yield. Also sp³-alkylzinc reagents such as cyclohexylzinc chloride (2b) and *n*-octylzinc chloride (2e) react cleanly with TMTD (1, 1 h, 25 °C). The corresponding dithiocarbamates 4b,c are obtained in excellent yields (86–91%; entries 2 and 5). Although the preparation of alkylthio derivatives can be often performed by a direct S_N 2 substitution, the reaction

SYNLETT 2006, No. 5, pp 0792–0794 Advanced online publication: 09.03.2006 DOI: 10.1055/s-2006-933117; Art ID: G39905ST © Georg Thieme Verlag Stuttgart · New York of TMTD with zinc organometallics has a real synthetic value in cases where the alkyl halide is sterically hindered and where an $S_N 2$ reaction is complicated by a competitive elimination reaction. Thus, β -pinene **5** is readily converted to the corresponding diorganozinc **3a** via a hydroboration and B–Zn exchange sequence.⁶ The reaction with TMTD (1) produces the chiral dithiocarbamate **4d** in 70% yield starting from β -pinene. Similarly, the hydroboration and B–Zn exchange reaction sequence of norbornene **6** gives the *exo*-diorganozinc species **3b**. Remarkably, the reaction of **3b** with TMTD (1) proceeds with complete retention of configuration providing the *exo*-dithiocarbamate **4e** in 81% yield (Scheme 2) as a single diastereomer.





Interestingly, the behavior of alkylzinc iodides compared to dialkylzincs in their reaction with TMTD is different. Thus, the direct reaction of 3-carbethoxypropylzinc iodide (**2l**), obtained by the reaction of zinc dust with ethyl 4-iodobutyrate (7)⁷ is complicated by a redox process tentatively formulated via a cyclic transition state in Scheme 3 and leads back to the starting alkyl iodide $7.^{8}$ On the other hand, the reaction of **2l** with the lithium salt (Me₂NCS₂Li)⁹ provides the alkylzinc thio derivative **8** which reacts as expected with TMTD (**1**, r.t., 1 h) giving the desired dithiocarbamate **4f** in 87% yield (Scheme 3).

This behavior seems to be general for organozinc iodides. Thus, cyclohexyl- (2d), *n*-octyl- (2g) and benzylzinc (2j) iodides were examined and after the reaction with TMTD (1) all of them gave back the starting alkyl iodides with >90% conversion and only traces (<3%) of dithiocarbamates were observed. However, subsequent reaction of these organozinc compounds with lithium salt (Me₂NCS₂Li) furnishes desired dithiocarbamates in good yields (entries 4, 7, 10).



Scheme 3

Table 1	Preparation of	Dimethyldithiocarbamates	through Zinc	Reagents
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Entry	Zinc reagent	Product of type 4	Yield (%) ^a
1	ZnCl 2a ^b	S S S	88
2	ZnX 2b: $X = Cl^b$	4a $()$ $()$ $()$ $()$ $()$ $()$ $()$ $()$	91
3	2c: $X = Br^c$	4b	89
4	$2d: X = I^{d,e}$	4b	83
5	n-OctZnX 2e: $X = Cl^b$	n -Oct $\sim S$ \bigvee_{S}^{N} \bigvee_{S}^{N} 4c	94
6	2f: $X = Br^c$	4c	87
7	2g: $X = I^{d,e}$	4c	80
8	ZnBr 2h ^c	Je Sector S	79
9	ZnX 2i: X = Br ^d		84
10	$2j: X = I^{d,e}$	4f	77
11	O ZnBr 2k ^{d,e}	∠OS_N 4g	84

^a Isolated yield of analytically pure product.

^b Prepared by Mg–Zn transmetalation with ZnCl₂ (1 M in THF). ^c Prepared by Mg–Zn transmetalation with ZnBr₂ (1 M in THF).

^d Prepared by the direct insertion of Zn dust in THF.

 e 1 equiv of Me_2NCS_2Li was added before reaction with TMTD (1).

Surprised with these results, we also examined reactions of organozinc bromides with TMTD (1). Indeed, they behave similar to the organozinc chlorides and afford dithiocarbamates **4b–c** and **4e–f** in comparable yields. No alkyl bromides were detected. Also, ambident nucleophiles like the Reformatsky reagent (**2k**), generated by direct insertion of zinc dust into bromoacetic acid ethyl ester, reacts cleanly with TMTD (1) exclusively as C-nucleophile, furnishing the derivative of thioacetic acid (**4g**) in 82% yield (entry 11).

In summary, we have shown that various classes of organozinc compounds react with TMTD (1) affording the corresponding dithiocarbamates. The use of diorganozinc derivatives gave the best results and very good yields were obtained in all cases. This reaction can be further extended to readily available functionalized alkyl zinc reagents and proceeds with retention of configuration. Extensions of this method are currently underway in our laboratories.¹⁰

Acknowledgment

We thank the Fonds der Chemischen Industrie and Merck Research Laboratories (MSD) for financial support. We thank Chemetall GmbH (Frankfurt), BASF AG (Ludwigshafen) and Lanxess AG for generous gifts of chemicals.

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- (8) This new redox reaction is actively investigated in our laboratories.
- (9) This lithium salt is readily prepared by treating TMTD (1) in THF with MeLi (1 equiv, -20 °C, 10 min).
- (10) Typical Procedure: Preparation of Myrtanyl Dimethyldithiocarbamate (4d). A 25-mL Schlenk flask containing a solution of TMTD (1.00 g, 4.16 mmol) in CH₂Cl₂ (5 mL) was cooled to 0 °C, and bis(myrtanyl)zinc (510 mg, 1.5 mmol)⁶ was added slowly at this temperature. The reaction mixture was stirred for 20 h at r.t. (a white precipitate of zinc dimethyldithiocarbamate formed), then was diluted with Et₂O (30 mL) and filtered. The precipitate was washed with Et₂O, the filtrate evaporated and the residue was purified by column chromatography (pentane–CH₂Cl₂), yielding myrtanyl dimethyldithiocarbamate as colorless crystals, mp 30–31 °C (70% yield, 673 mg).