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Direct Transformation of Allylic and Benzylic Thiols, Thioethers, and Disulfides into Organolithium Compounds

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Direct Transformation of Allylic and Benzylic Thiols, Thioethers, and Disulfides into Organolithium Compounds

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ABSTRACT

The reaction of allylic and benzylic thiols 1, disulfides 3, and thioethers 4 and 5 with an excess of lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5 mol%) afforded the corresponding allylic and benzylic organolithium reagents via reductive cleavage of the carbon–sulfur bond. The generated organolithium compounds gave the expected products 2 by reaction with several electrophiles followed by hydrolysis with water. The reaction conditions and the lithiation procedure (stepwise of Barbier-type process) depended on the starting sulfur containing compound.

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Key Words: Lithium; Organolithium; Thiol; Sulfide; Disulfide; Carbon-sulfur bond cleavage.

1. INTRODUCTION

In recent years, the chemistry of organosulfur compounds has attracted much attention to organic chemists. Several research groups have contributed to the development of methods of synthesis of thiols and sulfides and to the knowledge of their reactivity.^[1–3] Reductive cleavage of the carbon–sulfur bond in thiols may be performed by several reagents,^[4] but, to the best of our knowledge, it always leads to reduction to the corresponding hydrocarbons. In order to achieve the functionalization of the carbon atom that initially was bearing the sulfur atom, mercaptans can be transformed into alkyl halides^[5] or phenyl sulfides,^[6] which are suitable precursors of alkyllithium reagents.^[7,8] However, it would be very interesting from a synthetic point of view to be able to achieve the direct conversion of a thiol into an organolithium compound.

In the last few years, we have been using an arene-catalyzed lithiation^[9,10] to prepare a variety of organolithium compounds,^[11–14] including allylic and benzylic organolithium reagents.^[13–16] Some years ago, we reported on the direct transformation of allylic and benzylic alcohols into the corresponding organolithium reagents.^[15c] Since the carbon–sulfur bond is weaker than the carbon–oxygen bond,^[17] we decided to try the same transformation from allylic and benzylic thiols, the process having also been extended to the corresponding disulfides and thioethers.

2. RESULTS AND DISCUSSION

When benzyl mercaptan **1a** (Sch. 1) was deprotonated with *n*-butyllithium and the obtained thiolate was treated with an excess of lithium powder and a catalytic amount of DTBB at 0°C, followed by addition of an electrophile at -30° C, the expected products **2aa–2ae** were obtained in moderate to good yields (Table 1, Entries 1–5). However, when the lithiation of 1-phenylethyl mercaptan **1b** was carried out using 3-pentanone or pivalaldehyde as electrophiles, an intractable mixture of compounds was obtained from which the expected products could not be separated.

The reaction with allyl mercaptan 1c (Sch. 1) had to be performed at room temperature during 3 h in order to complete the reductive cleavage. However, only a very small amount of the expected products was formed after the addition of benzaldehyde or cyclohexanone as electrophiles. We decided to test geranyl mercaptan 1d (Chart 1), in order to check if the

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Allylic a	nd Be	nzylic	Thiols,	Thioethers,	and	Disulfides
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Table 1. DTBB-catalyzed lithiation of thiols 1, disulfides 3, and sulfides 4 and 5.

			Product ^a				
Entry	Substrate	Electrophile	No.	R	Ε	Yield (%) ^b	
1	1a	Me ₃ SiCl	2aa	PhCH ₂	Me ₃ Si	59	
2	1a	Bu ^t CHO	2ab	PhCH ₂	Bu ^t CHOH	48	
3	1a	PhCHO	2ac	PhCH ₂	PhCHOH	65	
4	1a	Et ₂ CO	2ad	PhCH ₂	Et ₂ COH	43	
5	1a	(CH ₂) ₅ CO	2ae	PhCH ₂	(CH ₂) ₅ COH	49	
6	3a	Me ₃ SiCl	2aa	PhCH ₂	Me ₃ Si	$40^{\rm c}$	
7	3a	Bu ^t CHO	2ab	PhCH ₂	Bu ^t CHOH	48 ^c	
8	3a	Et ₂ CO	2ad	PhCH ₂	Et ₂ COH	23°	
9	3b	Me ₃ SiCl	2ba	Geranyl	Me ₃ Si	38 ^c	
10	4 a	PhCHO	2ac	PhCH ₂	PhCHOH	67	
11	4 a	Et ₂ CO	2ad	PhCH ₂	Et ₂ COH	50	
12	4 b	PhCHO	2ca	CH ₂ =CHCH ₂	PhCHOH	59	
13	4 b	Pr_2^nCO	2cb	CH ₂ =CHCH ₂	Pr ⁿ ₂ COH	35	
14	5a	Me ₃ SiCl	2aa	PhCH ₂	Me ₃ Si	33 ^c	
15	5a	Bu ^t CHO	2ab	PhCH ₂	Bu ^t CHOH	26 ^c	
16	5a	Et ₂ CO	2ad	PhCH ₂	Et ₂ COH	36 ^c	

^aAll compounds **2** were \geq 95% pure (GLC and/or 300 MHz ¹H NMR).

^bIsolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material 1, 3, 4, or 5.

^cIsolated yield based on the starting material 3 or 5 corresponding to the stoichiometry 3 (or 5) \rightarrow 2 2.



Scheme 1. Reagents and conditions: (i) Bu^nLi , THF, 20°C; (ii) Li, DTBB (5 mol %), THF, 0°C (for 1a and 1b) or 20°C (for 1c); (iii) $E^+=Me_3SiCl$, Bu^tCHO , PhCHO, Et_2CO , (CH₂)₅CO, THF, -30 to 0°C; (iv) H₂O.

reduction of the allylic organolithium reagent was the preferred pathway in this case. We found some problems in the preparation of **1d**, since it was oxidized to some extent to the corresponding disulfide **3b** (Chart 1) during the work-up.^[18] A mixture of thiol and disulfide was obtained, which could not be separated. This mixture was submitted to oxidation with sodium hypochlorite and digeranyl disulfide **3b** was exclusively obtained. NI-

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DTBB-catalyzed lithiation of **3b** at 20° C for 2.5 h, followed by addition of trimethylsilyl chloride at -30° C, led to the expected product **2ba** in 38% yield based on the starting disulfide for the formation of 2 equiv. of geranyllithium (Chart 1, Sch. 2, Table 1, Entry 9, footnote c). However, when 3-pentanone was used as electrophile, only a very small amount of the expected alcohol **2bd** (Chart 1) was formed,^[19] the major product being the one resulting from sulfur–hydrogen exchange (GC–MS). We also tried the lithiation of commercially available diallyl disulfide, but it failed. We think that the long reaction time and the high temperature necessary to achieve the carbon–sulfur bond cleavage could cause the decomposition of the generated allylic organolithium reagents by proton abstraction from the reaction medium.^[20] This behavior could also be the reason for the failure of the lithiation of allyl mercaptan **1c**.

Dibenzyl disulfide **3a** (Sch. 2) was also submitted to the DTBB-catalyzed lithiation process at 0° C and, after addition of the corresponding electrophile at -30° C, the expected products **2aa**, **2ab**, and **2ad** were obtained in moderate yields (Sch. 2, Table 1, Entries 6–8, footnote c).







Scheme 2. Reagents and conditions: (i) Li, DTBB (5 mol%), THF, 0°C (for 3a) or 20°C (for 3b); (ii) $E^+ = Me_3SiCl$, Bu'CHO, Et_2CO , THF, -30 to 0°C; (iii) H_2O ; (iv) Li, DTBB (5 mol%), $E^+ = Me_3SiCl$, PhCHO, Et_2CO , (CH₂)₅CO, Pr_2^nCO , THF, 0°C.

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In the second part of this study, we decided to investigate if some other sulfides different from the commonly used phenyl sulfides could be utilized as sources of allyl- and benzyllithium. The reaction of benzyl methyl sulfide **4a** (Sch. 2) with an excess of lithium and a catalytic amount of DTBB in THF at 0°C in the presence of benzaldehyde or 3-pentanone [Barbier-type reaction conditions^[21]] gave the expected addition products **2ac** and **2ad** in 67% and 50% yield, respectively (Sch. 2, Table 1, Entries 10 and 11). Commercially available allyl methyl sulfide **4b** (Sch. 2) was also tested as starting material. The DTBB-catalyzed lithiation of **4b** under the reaction conditions described above for sulfide **4a** gave the expected products in moderate to good yields (Sch. 2, Table 1, Entries 12 and 13).

We thought that the lithiation of dibenzyl sulfide **5a** (Sch. 2) could lead us to the generation of 2 equiv. of benzyllithium. Sulfide **5a** was submitted to a DTBB-catalyzed lithiation reaction at 0°C in the presence of several electrophiles and the expected products were formed in moderate yields, assuming that the stoichiometry of the reaction is $5a \rightarrow 2 2$ (Table 1, Entries 14–16). As occurred for allyl mercaptan and diallyl disulfide, the reductive cleavage of diallyl sulfide **5b** had to be performed at 20°C, but it did not afford the expected addition products. A likely explanation for this could be the decomposition of the generated allyllithium by proton abstraction from the reaction medium^[20] due to the temperature used in the process.

3. CONCLUSIONS

In this article, we have proven that allylic and benzylic thiols, sulfides and disulfides can directly be transformed into the corresponding organolithium reagents. The lithiation of allyl methyl sulfide and benzyl methyl sulfide has proved to be a good alternative to the reductive cleavage of the commonly used phenyl sulfides for the generation of allyl- and benzyllithium, respectively. Although yields are moderate, the DTBBcatalyzed lithiation of benzylic substrates represents a new method for the preparation of benzyllithium from non-halogenated materials.

4. EXPERIMENTAL

4.1. General

For general information, see Ref.^[15k] Thiols **1a** and **1c**, disulfide **3a**, sulfides **4a**, **4b**, **5a**, and **5b**, DTBB and all the electrophilic reagents were commercially available (Aldrich, Acros) and were used as received, with

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the exception of benzaldehyde, which was distilled before use. Lithium powder was prepared according to the procedure described in Ref.^[15 k] Commercially available *n*-butyllithium was titrated with a 1 M solution of *sec*-butanol in xylene using 1,10-phenanthroline as indicator,^[22] THF was dried over sodium benzophenone ketyl under an argon atmosphere and distilled before use. 1-Phenylethanethiol (**1b**)^[23] and digeranyl disulfide (**3b**)^[24] were prepared according to literature procedures and were fully characterized by spectroscopic means.

4.2. Lithiation of Thiols 1 and Reaction with Electrophiles. Isolation of Compounds 2

n-Butyllithium (0.66 mL of a 1.6 M solution in hexane, 1.1 mmol) was added dropwise to a solution of the corresponding thiol 1 (1.0 mmol) under argon at 20°C. After 5 min, the resulting lithium thiolate solution was added dropwise to a green suspension of lithium powder (70 mg, 10.0 mmol) and DTBB (27 mg, 0.1 mmol) in THF (5 mL) under argon at 0° C (for **1a** and **1b**) or 20° C (for **1c**) and the reaction mixture was stirred for 1 h (for 1a and 1b) or 3 h (for 1c). After cooling to -30° C, the corresponding electrophile (1.2 mmol) was added dropwise and the mixture was stirred for ca. 3 h allowing the temperature to rise to 0° C. The reaction was then hydrolyzed with water (10 mL), acidified with 2 M HCl, and extracted with ethyl acetate $(3 \times 20 \text{ mL})$. The combined organic layers were successively washed with a saturated solution of NaHCO₃ (5 mL), water (5 mL), and brine (5 mL), being then dried (Na₂SO₄). After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield products 2aa-2ae in the yields indicated in Table 1. Compounds 2aa,^[15b] 2ab,^[15e] and 2ac-2ae,^[15a] previously prepared in our laboratory, were identified by comparison of their spectroscopic data with authentic samples.

4.3. Lithiation of Disulfides 3 and Reaction with Electrophiles. Isolation of Compounds 2

A solution of disulfide **3** (1.0 mmol) in THF (2 mL) was added dropwise to a green suspension of lithium powder (70 mg, 10.0 mmol) and DTBB (27 mg, 0.1 mmol) in THF (5 mL) under argon at 0°C (for **3a**) or 20°C (for **3b**) and the reaction mixture was stirred for 1 h (for **3a**) or 2.5 h (for **3b**). After cooling to -30° C, the corresponding electrophile (2.4 mmol) was added dropwise and the mixture was stirred for ca. 3 h allowing the temperature to rise to 0°C. The reaction was then hydro-

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lyzed with water (10 mL), acidified with 2 M HCl, and extracted with ethyl acetate ($3 \times 20 \text{ mL}$). The combined organic layers were successively washed with a saturated solution of NaHCO₃ (5 mL), water (5 mL), and brine (5 mL), being then dried (Na₂SO₄). After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield products **2aa**, **2ab**, **2ad**, and **2ba** in the yields indicated in Table 1. Compounds **2aa**,^[15b] **2ab**,^[15e] **2ad**,^[15a] and **2ba**^[15c] previously prepared in our laboratory, were identified by comparison of their spectroscopic data with authentic samples.

4.4. Lithiation of Sulfides 4 and 5 Under Barbier-Type Reaction Conditions. Isolation of Compounds 2

To a green suspension of lithium powder (70 mg, 10.0 mmol) and DTBB (27 mg, 0.1 mmol) in THF (5 mL) under argon at 0°C was added dropwise a solution of sulfide **4** or **5** (1.0 mmol) and the corresponding electrophile (2.4 mmol) in THF (2 mL) during ca. 1 h using a syringe pump. After the addition was complete, the reaction mixture was stirred for ca. 2 h at the same temperature. The reaction was then hydrolyzed with water (10 mL), acidified with 2 M HCl, and extracted with ethyl acetate (3×20 mL). The combined organic layers were successively washed with a saturated solution of NaHCO₃ (5 mL), water (5 mL), and brine (5 mL), being then dried (Na₂SO₄). After evaporation of the solvents (15 Torr) the resulting residue was purified by column chromatography (silica gel, hexane) to yield products **2aa**, **2ac**, **2ad**, **2ca**, and **2cb** in the yields indicated in Table 1. Compounds **2aa**,^[15b] **2ac**,^[15a] **2ad**,^[15a] **2ca**,^[15a] and **2cb**,^[25] previously prepared in our laboratory, were identified by comparison of their spectroscopic data with authentic samples.

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