# DTBB-Catalyzed Lithiation of 4-Hetero-substituted Dibenzothiins

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The DTBB-catalyzed lithiation of 4-hetero-substituted dibenzothiins (phenoxathiin, phenothiazine, and thianthrene) gives the corresponding functionalized organolithium intermediates, which by reaction with different electrophiles afford the expected functionalized thiols. The cyclization of some alcohol compound derivatives gives the corresponding homologous seven-membered dibenzo heterocycles.

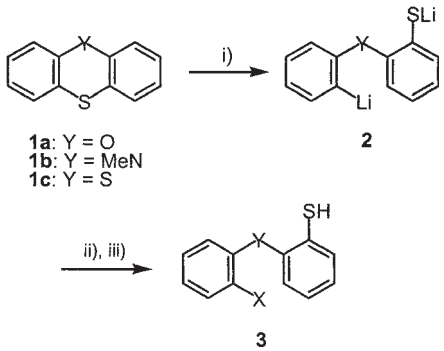
The versatility of organolithium compounds[1] in synthetic organic chemistry is greatly enhanced when the intermediate contains a functional group in its structure[2] because, by reaction with electrophiles, this type of compounds affords directly polyfunctionalized molecules. Among different methodologies to prepare functionalized organolithium compounds, the reductive opening of heterocycles represents one of the most useful one.[3,4] On the other hand, in the last few years we have been using an arene-catalyzed lithiation reaction[5–9] to prepare unstable organolithium compounds under very mild reaction conditions. In addition, the cleavage of the carbon-sulfur bond in phenylthioethers using either the stoichiometric[10] or the catalytic version of the arene-mediated lithiation[6] has been used to generate organolithium compounds by sulfur-lithium exchange. The application of the arene-catalyzed version to some sulfur-containing heterocycles such as thietanes,[12] tetrahydrothiophenes,[12,13] tetrahydrothiopyrans,[12] and 2,7-dihydrodibenzoazepine[14] allows the direct preparation of functionalized organolithium compounds.[2] In this paper we report on the application of the mentioned lithiation methodology to the reductive ring opening of 4-hetero-substituted dibenzothiins.

The reaction of phenoxathiin (**1a**) with lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 7.5 mol%) in THF at −78 °C gave the corresponding intermediate **2** (Y=O), which after reacting with different electrophiles [$H_2O$, $D_2O$, $Bu^tCHO$, PhCHO, $Me_2CO$, $Et_2CO$, $(CH_2)_5CO$] at the same temperature and final hydrolysis with hydrochloric acid, afforded the expected functionalized thiols **3a–g** (Scheme 1 and Table 1, entries 1–7.)

When the process shown in Scheme 1 was applied to phenothiazine (**1b**) and thianthrene (**1c**), the corresponding products **3h–k** and **3l–n** were, respectively, obtained, intermediates **2** (Y=MeN, S) being probably involved in the reaction.

Some selected functionalized thiols **3d**,**f**,**m**,**n**, derived from carbonyl compounds, were cyclized under acidic conditions (85% phosphoric acid under toluene reflux)[14] to give the corresponding seven-membered dibenzo compounds **4**. From a synthetic point of view, the whole process **1**→**4** represents a homologation of the starting materials **1** (Scheme 2 and Table 2). In this reaction, the corresponding benzylic carbenium ion is probably involved, which after intramolecular nucleophilic attack by the sulfur atom gives the final heterocycles **4**.[15]

In conclusion, we have shown in this paper that the DTBB-catalyzed lithiation of dibenzo heterocycles **1** is a versatile way to

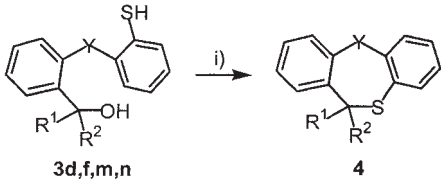



**Scheme 1.** Reagents and conditions: i) Li, DTBB (7.5 mol%), THF, −78 (for **1a**) or −90 °C (for **1b**, **c**); ii) E = $H_2O$, $D_2O$, $Bu^tCHO$, PhCHO, $Ph(CH_2)_2CHO$, $Me_2CO$, $Et_2CO$, $(CH_2)_5CO$, −78 °C; iii) 3 M HCl, −78 °C to rt.

**Table 1.** Preparation of compounds **3**

| Run | Start. mat. | Electrophile | Product[a] No. | Product[a] X | Product[a] Yield/%[b] |
|---|---|---|---|---|---|
| 1 | **1a** | $H_2O$ | **3a** | H | 50 |
| 2 | **1a** | $D_2O$ | **3b** | D | 53[c] |
| 3 | **1a** | $Bu^tCHO$ | **3c** | $Bu^tCHOH$ | 63 |
| 4 | **1a** | PhCHO | **3d** | PhCHOH | 49 |
| 5 | **1a** | $Me_2CO$ | **3e** | $Me_2COH$ | 82 |
| 6 | **1a** | $Et_2CO$ | **3f** | $Et_2COH$ | 44 |
| 7 | **1a** | $(CH_2)_5CO$ | **3g** | $(CH_2)_5COH$ | 41 |
| 8 | **1b** | $H_2O$ | **3h** | H | 95 |
| 9 | **1b** | $Bu^tCHO$ | **3i** | $Bu^tCHOH$ | 25 |
| 10 | **1b** | PhCHO | **3j** | PhCHOH | 64 |
| 11 | **1b** | $Ph(CH_2)_2CHO$ | **3k** | $Ph(CH_2)_2CHOH$ | 48 |
| 12 | **1c** | $H_2O$ | **3l** | H | 98 |
| 13 | **1c** | $Bu^tCHO$ | **3m** | $Bu^tCHOH$ | 39 |
| 14 | **1c** | PhCHO | **3n** | PhCHOH | 52 |

[a]All products **3** were >95% pure (300 MHz $^1H$ NMR and/or GLC) and were fully characterized by spectroscopic means (IR, $^1H$ and $^{13}C$ NMR, and MS). [b]Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting heterocycle **1**. [c]>90% deuterium incorporation (MS).




**Scheme 2.** Reagents and conditions i) 85% $H_3PO_4$, PhMe, 110 °C.

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**Table 2.** Preparation of compounds **4**

| Run | Starting material | Product[a] | | | | |
|---|---|---|---|---|---|---|
| | | No. | Y | $R^1$ | $R^2$ | Yield/%[b] |
| 1 | **3d** | **4d** | O | Ph | H | 78 |
| 2 | **3f** | **4f** | O | Et | Et | 85 |
| 3 | **3m** | **4m** | S | Bu[1] | H | 74 |
| 4 | **3n** | **4n** | S | Ph | H | 97 |

[a]All products **4** were >95% pure (300 MHz $^1$H NMR and/or GLC) and were fully characterized by spectroscopic means (IR, $^1$H and $^{13}$C NMR, and MS). [b]Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **3**.

prepare functionalized organolithium compounds in a direct manner, which react with electrophiles giving functionalized molecules, susceptible to generate homologated heterocycles by cyclization under acidic conditions.[16]

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16 Typical procedure for compounds **3**: To a suspension of lithium powder (100 mg, 14 mmol) and DTBB (40 mg, 0.15 mmol; 7.5 mol%) in THF (4 mL) was added dropwise a solution of phenoxathiin (0.40 g, 2 mmol) in THF (0.5 mL) at −78 °C. The resulting mixture was stirred 45 min at the same temperature, being then quenched with the corresponding electrophile (2.4 mmol; 0.5 mL in the case of $H_2O$ and $D_2O$). After 15 min stirring at −78 °C, the mixture was hydrolyzed with water (10 mL) allowing the temperature to rise to rt. The resulting mixture was extracted with ether (3 × 25 mL), the aqueous layer was acidified with 3 M hydrochloric acid and extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over $MgSO_4$, evaporated under vacuum (15 Torr) and the resulting residue purified by column chromatography (silica gel, hexane/ethyl acetate) to yield the expected pure product **3**.