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# DTBB-catalysed lithiation of 1,7-dihydrodibenzothiepin

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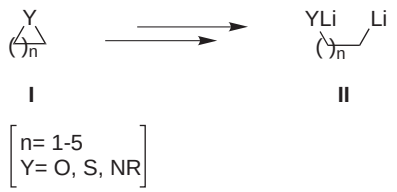
**Abstract**—Treatment of 1,7-dihydrodibenzothiepin (**1**) with an excess of lithium powder and a catalytic amount of DTBB (5 mol%) at −78°C for 30 min followed by reaction with a carbonyl compound {$^t$BuCHO, $Ph(CH_2)_2CHO$, PhCHO, $Me_2CO$, $[Me(CH_2)_4]_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone} at the same temperature led, after hydrolysis with 3N hydrochloric acid, to sulfenyl alcohols **4**. When alkoxide **3**, which is formed after addition of the first carbonyl compound [$Me_2CO$, $(CH_2)_5CO$, (−)-menthone], is stirred at room temperature for 30 min, a new lithiation occurred and after addition of a second electrophile [$Me_2CO$, $Et_2CO$, $(CH_2)_5CO$, $ClCO_2Et$] and final hydrolysis with water, difunctionalised biphenyls **6** are formed. Treatment of the sulfenyl alcohol **4c** with 85% phosphoric acid in toluene at reflux for 4 h gave the sulfur-containing eight-membered heterocycle **8c** in good yield. 

When an organolithium compound[1] bears a functional group,[2] its reaction with an electrophilic reagent allows the direct generation of polyfunctionalised molecules through transfer of the functionality to the electrophile. Among the methodologies for the generation of these intermediates, the halogen–lithium exchange[3] or the reductive ring opening of heterocycles[4] are the most important procedures. In the second case, depending on the size of the heterocyclic precursor **I** and the type of heteroatom,[4] different functionalised organolithium compounds **II** are accessible. Thus, starting from three-,[5] four-,[6] five-,[7] or six-membered[8] heterocyclic materials, β-, γ-, δ- or ε-functionalised organolithium intermediates[9] can be prepared. Very recently, one paper regarding the generation of the corresponding functionalised organolithium compounds through the reductive opening of oxygen- and nitrogen-containing seven-membered rings has been reported.[10] On the other hand, and in order to get a potent lithiation agent at low temperatures, we found out some years ago[11] that the use of a substoichiometric amount of an arene [mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)][12] catalysed the lithiation reaction, making possible new processes under very mild reaction conditions.[13–15] In this paper we report the application of the DTBB-catalysed lithiation to the ring opening of a sulfur-containing seven-membered ring, namely 1,7-dihydrodibenzothiepin (**1**), in order to study the possibility of introducing one or two (equal or different) electrophilic fragments at the 2- and 2′-benzylic positions of the biphenyl skeleton.




The reaction of 1,7-dihydrodibenzothiepin (**1**) [easily prepared from commercially available 2,2′-bis(bromomethyl)biphenyl and sodium sulfide nonahydrate at 100°C in DMF in almost quantitative yield][16] with an excess of lithium and a catalytic amount of DTBB (5 mol%) in THF at −78°C led, after 30 min, to a solution of the dianion **2**, which reacted with different electrophilic reagents {$^t$BuCHO, $Ph(CH_2)_2CHO$, PhCHO, $Me_2CO$, $[Me(CH_2)_4]_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone} at the same temperature for 5 min yielding dianionic species **3**, which after hydrolysis with 3N hydrochloric acid gave the expected sulfenyl alcohols **4** (Scheme 1 and Table 1, entries 1–8). In the case of using prochiral carbonyl compounds such as aldehydes or (−)-menthone, an almost 1:1 diastereomeric mixture of sulfenyl alcohols **4** was obtained (Table 1, entries 1–3 and 8) due to the presence of a stereogenic axis in the 2,2′-disubstituted biphenyl moiety. With (−)-menthone as the electrophile, the attack of dianion **2** took place almost exclusively from the less hindered face of the carbonyl group (Fig. 1).

*Keywords*: sulfur/lithium exchange; DTBB-catalysed lithiation; functionalised biphenyls.

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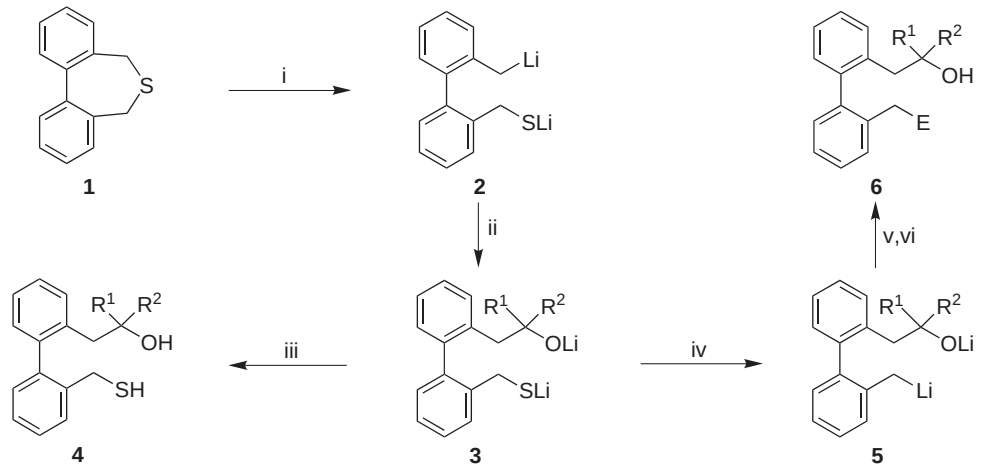



**Scheme 1.** *Reagents and conditions*: (i) Li, DTBB (5 mol%), THF, −78°C, 30 min; (ii) $R^1R^2CO = {}^tBuCHO$, $Ph(CH_2)_2CHO$, PhCHO, $Me_2CO$, $[Me(CH_2)_4]_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone, −78°C, 5 min; (iii) 3N HCl, −78 to 20°C; (iv) 20°C, 30 min; (v) $E^+ = Me_2CO$, $Et_2CO$, $(CH_2)_5CO$, $ClCO_2Et$, −78°C, 5 min; (vi) $H_2O$, −78 to 20°C.

**Table 1.** Preparation of compounds **4** and **6**

| Entry | $R^1R^2CO$ | $E^+$ | Product[a] | | | |
|---|---|---|---|---|---|---|
| | | | No. | $R^1R^2COH$ | E | Yield (%)[b] |
| 1 | ${}^tBuCHO$ | – | **4a** | ${}^tBuCHOH$ | – | 71[c] |
| 2 | $Ph(CH_2)_2CHO$ | – | **4b** | $Ph(CH_2)_2CHOH$ | – | 75[c] |
| 3 | PhCHO | – | **4c** | PhCHOH | – | 82[c] |
| 4 | $Me_2CO$ | – | **4d** | $Me_2COH$ | – | 50 |
| 5 | $[Me(CH_2)_4]_2CO$ | – | **4e** | $[Me(CH_2)_4]_2COH$ | – | 76 |
| 6 | $(CH_2)_5CO$ | – | **4f** | $(CH_2)_5COH$ | – | 72 |
| 7 | $(CH_2)_7CO$ | – | **4g** | $(CH_2)_7COH$ | – | 47 |
| 8 | (−)-Menthone | – | **4h**[d] | – | – | 55[c] |
| 9 | $Me_2CO$ | $Me_2CO$ | **6da** | $Me_2COH$ | $Me_2COH$ | 40 |
| 10 | $Me_2CO$ | $ClCO_2Et$ | **6dd** | $Me_2COH$ | $CO_2Et$ | 36 |
| 11 | $(CH_2)_5CO$ | $Me_2CO$ | **6fa** | $(CH_2)_5COH$ | $Me_2COH$ | 45 |
| 12 | $(CH_2)_5CO$ | $Et_2CO$ | **6fb** | $(CH_2)_5COH$ | $Et_2COH$ | 46 |
| 13 | $(CH_2)_5CO$ | $(CH_2)_5CO$ | **6fc** | $(CH_2)_5COH$ | $(CH_2)_5COH$ | 38 |
| 14 | $(CH_2)_5CO$ | $ClCO_2Et$ | **6fd** | $(CH_2)_5COH$ | $CO_2Et$ | 41 |
| 15 | (−)-Menthone | $Me_2CO$ | **6ha**[d] | – | $Me_2COH$ | 35[c] |

[a] All products were >95% pure (GLC and 300 MHz $^1H$ NMR) and were fully characterised by spectroscopic means (IR, $^1H$ and $^{13}C$ NMR, and mass spectrometry).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting compound **1**.
[c] Isolated as a ca. 1:1 diastereomeric mixture ($^1H$ and $^{13}C$ NMR).
[d] See Fig. 1.

The lithiation of 1,7-dihydrodibenzothiepin (**1**) can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. Thus, once the first lithiation took place, giving the intermediate **2**, this dianion was allowed to react first with a carbonyl compound [$Me_2CO$, $(CH_2)_5CO$, (−)-menthone] at −78°C, the resulting alkoxide **3** was stirred at room temperature for 30 min, so a second lithiation occurred with the excess of lithium still present in the reaction medium, giving a new functionalised organolithium compound **5**, which finally reacted with a second electrophile [$Me_2CO$, $Et_2CO$, $(CH_2)_5CO$, $ClCO_2Et$] at −78°C giving, after hydrolysis with water, the corresponding difunctionalised biphenyls **6** (Scheme 1 and Table 1, entries 9–15).

In order to check the synthetic utility of this methodology, the sulfenyl alcohol **4c** and the diol **6fc** were treated with 85% phosphoric acid in toluene at reflux for 4 h. In the case of **4c**, the sulfur-containing eight-membered heterocycle **8c** was obtained in good yield;

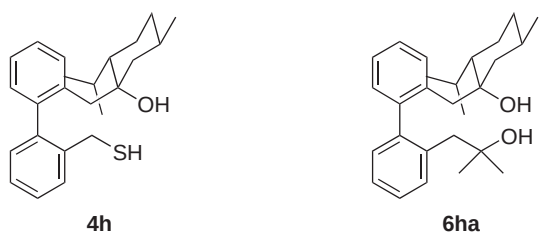
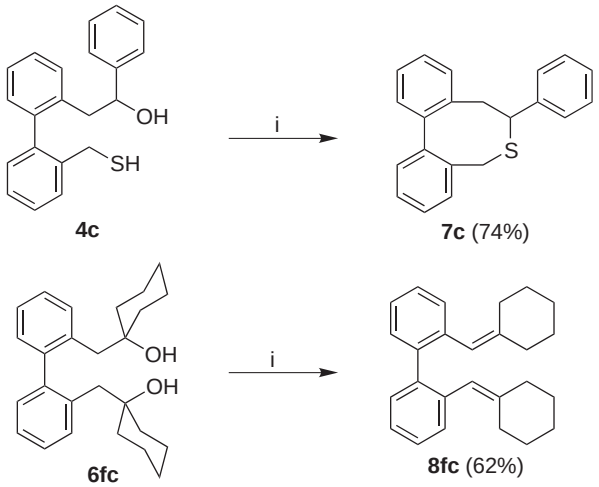
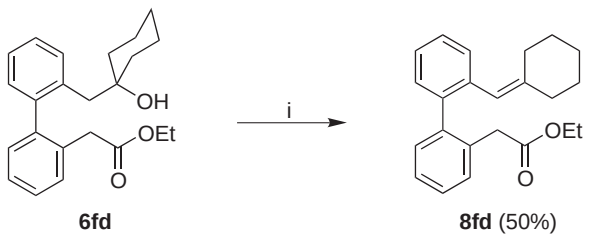



**Figure 1.**




**Scheme 2.** *Reagents and conditions*: (i) $H_3PO_4$ (85%), PhMe, 110°C, 4 h.




**Scheme 3.** *Reagents and conditions*: (i) TsOH (cat.), PhMe, 110°C, 4 h.

however, the diol **6fc** did not lead to the oxygenated heterocycle but the conjugate diolefin **8fc** resulted from a double dehydration (Scheme 2).

Similarly, the hydroxy ester **6fd** was treated with a catalytic amount of *p*-toluenesulfonic acid in toluene at reflux for 4 h. The expected nine-membered lactone was not isolated, compound **8fd** being the major isolated reaction product in this case (Scheme 3).

From the results described here, we conclude that sulfenyl alcohols **4** and difunctionalised biphenyls **6** can be readily accessible from 1,7-dihydrodibenzothiepin (**1**) through a tandem monolithiation reaction with electrophiles or a double sequential lithiation reaction with electrophiles, respectively. It is noteworthy that the double lithiation process (giving intermediates of type **5**) has not been observed for the corresponding oxygen- or nitrogen-containing heterocyclic compounds of type **1**.[10] Finally, the sulfenyl alcohols **4** can be precursors of the corresponding sulfur-containing eight-membered rings through a dehydration process.

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