Base-Induced Ring Opening of Aza- and Thiaoxa[3.2.1] and -[3.3.1]bicycles as an Enantioselective Approach to Azepines, Thiepines, and Thiocines

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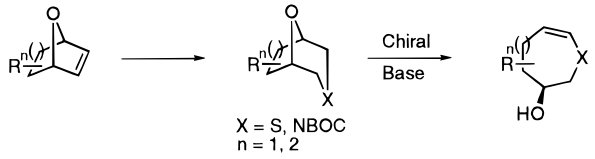
Medium-sized heterocycles are an important class of compounds which occur in a range of natural and unnatural products.[1−3] There is a need for a flexible and practical stereoselective method of forming medium ring nitrogen and sulfur heterocycles, which are useful synthetic intermediates as well as therapeutic agents.[1,2] Our approach to azepine, thiepine, and thiocine involves a desymmetrization of meso [3.2.1] and [3.3.1] aza- and thiaoxabicyclic systems via a deprotonation/C−O bond elimination sequence (Scheme 1).[4]

This communication describes our preliminary results on the enantioselective base-induced ring opening of hetero-oxabicyclic [3.2.1] and [3.3.1] systems for the facile construction of sulfur and nitrogen medium-sized heterocycles.

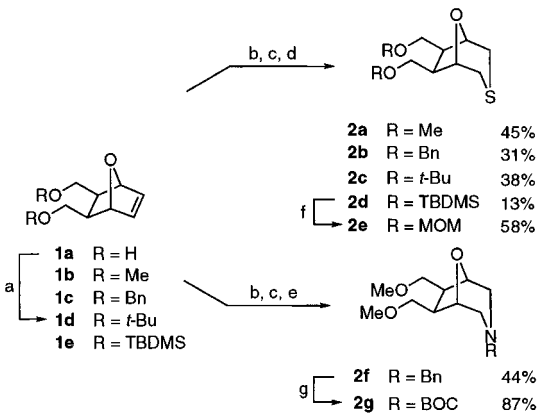
There are scattered reports in the literature describing the preparation of 3-aza- and 3-thia-8-oxa[3.2.1]bicycles.[5] We have developed a simple and versatile route to these compounds in five to six steps from the cycloadduct of furan and maleic anhydride.

The sequence begins with the oxa[2.2.1]bicycles **1a**−**e** and leads to the final [3.2.1]bicycles without purification of the diol and ditosylate.[6a,b] Three straightforward steps were required for the incorporation of the heteroatom moiety: ozonolysis and reduction,[7] and ditosylation followed by a double displacement of *p*-toluenesulfonate with Na_2S or benzylamine (Scheme 2).[5c−f,8,9] The reported

Scheme 1

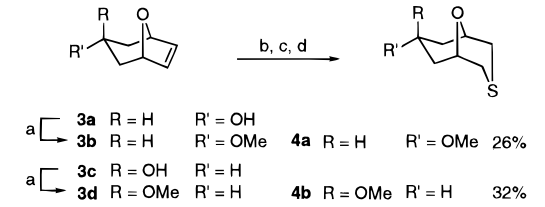


Scheme 2



(a) 2-Methylpropene, Amberlyst® 15 ion-exchange resin, hexanes-CH_2Cl_2, rt, 51%. (b) O_3, EtOH, 0 °C; $NaBH_4$. (c) TsCl, pyridine, rt. (d) Na_2S-$9H_2O$, DMF or EtOH/H_2O, reflux. (e) $BnNH_2$, $NaHCO_3$, DMF, reflux. (f) TBAF, THF; MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2. (g) Pd/C, HCO_2NH_4, $(BOC)_2O$, EtOH, rt.

Scheme 3



(a) NaH, MeI, 82% and 85%. (b) O_3, EtOH, 0 °C; $NaBH_4$. (c) TsCl, pyridine, rt. (d) Na_2S-$9H_2O$, DMF or EtOH/H_2O, reflux.

yields are for the three-step sequence and have been performed on a multigram scale (up to 20 g).

The oxathia[3.3.1]bicyclic substrates have been prepared via an identical route. The known oxa[3.2.1]bicyclic alcohols **3a**[6c] and **3c**[6d] were methylated, and the same sequence of steps led to the formation of the thiaoxa-[3.3.1]bicycles **4a** and **4b** (Scheme 3).

Our studies on the enantioselective deprotonation−elimination began by treating **2a** with 3 equiv of a lithium amide−LiCl complex (1:1) **5c** in THF generated from the hydrochloride salt of (−)-bis[(*S*)-1-phenylethyl]amine **5a** (Table 1, entry 1).[10] Replacement of THF with benzene dramatically increased not only the rate but also the enantioselectivity to give the thiepine **7a** in 91% yield and 89% ee after 1 h at ∼5 °C (Table 1, entry 2).[4a,11] The deprotonation−elimination failed at −78 °C in toluene, but at −50 °C, the substrate **2a** reacted with an increase of the ee from 89% to 95% (Table 1, entry 3). The use of a six-fold excess of base (or three-fold excess of base plus a three-fold excess of LiCl) was required to obtain a good yield of the desired opened product.[11] A pronounced LiCl effect was observed on the enantioselectivity of the deprotonation of **2a** in benzene at ∼5 °C; in the absence

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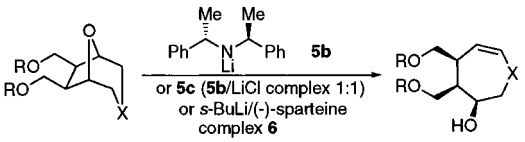
Table 1. Enantioselective Desymmetrization



Entry	Substrate		Base/Conditions[a]	Product	ee[b] %	Yield[c] %
1	**2a** R=Me	X=S	**5c**/THF/rt/24 h	**7a**	8	26[d]
2	**2a** R=Me	X=S	**5c**/PhH/5 °C/1 h	**7a**	89	91
3	**2a** R=Me	X=S	**5c**/$PhCH_3$/-50 °C/24 h	**7a**	95	79
4	**2b** R=Bn	X=S	**5c**/PhH/8 °C/10 h	**7b**	76	81
5	**2c** R=*t*-Bu	X=S	**5c**/PhH/rt/24 h	**7c**	---	NR
6	**2c** R=*t*-Bu	X=S	**5b**/PhH/rt/24 h	**7c**	43	76
7	**2d** R=TBDMS	X=S	**5c**/PhH/rt/24 h	**7d**	---	NR
8	**2e** R=MOM	X=S	**5c**/PhH/9 °C/10 h	**7e**	86	86
9	**2g** R=Me	X=NBOC	**6**/Et_2O/-78 °C/1 h	**7f**	46	95
10	**2g** R=Me	X=NBOC	**6**/Et_2O/-105 °C/1 h	**7f**	60	97

11	**4a** R=H	R'=OMe	**5c**/PhH/rt/40 h	**7g**	97	37
12	**4b** R=OMe	R'=H	**5c**/PhH/rt/48 h	**7h**	43	60

[a] See the Supporting Information for details. [b] Measured by preparing the Mosher ester or by capillary GC using a Chiraldex γ-TA column or by HPLC using a Chiralcel OD colomn. [c] Isolated yield of analytically pure product. [d] 68% Yield based on recovered starting material.

Table 2. LiCl Effect on the Deprotonation of 2a

LiCl, equiv	Chiral base **5b**, equiv	ee,[a] %	yield,[b] %
0	6	71	96
1	5	91	97
2	4	90	93
3	3	89	91

[a] Measured by capillary GC using a Chiraldex γ-TA column. [b] Isolated yield of analytically pure product.

of LiCl, the product **7a** was formed in 71% ee (Table 2).[12] For practical reasons, the remaining studies were conducted using the 1:1 lithium amide−LiCl complex **5c**. The absolute stereochemistry of **2a**, as illustrated in Table 1, was assigned by the Mosher method.[13]

Comparing the opening of **2b**, **2c**, **2d**, and **2e** with **2a** showed the dramatic effect of the remote hydroxy protecting groups on the reactivity, as well as on the enantioselectivity of the reaction (Table 1). The reduced reactivity of **2b**−**e** prevented us from lowering the temperature to improve the enantioselectivity. A protecting group capable of chelating appeared to be necessary. Treatment of the MOM-protected substrate **2e** with the base **5c** gave **7e** in similar ee and yield when compared to **2a** (Table 1, entries 2 and 8). However, a longer reaction time as well as a larger excess of base was necessary (6 equiv of base/LiCl) for the reaction to go to completion.

The BOC-protected nitrogen analog **2f** was treated with the preformed *s*-BuLi/(−)-sparteine complex **6** to give the azepine **7f** in good yields. The enantiomeric excess was 46% at −78 °C and 60% at −105 °C (Table 1, entries 9 and 10).[14,15]

The thia series was exclusively studied in the formation of eight-membered heterocycles. Reacting **4a** with **5c** for 40 h at rt afforded the thiocine **7g** in 97% ee although only 37% yield (Table 1, entry 11). The isomer **4b**, submitted to the identical conditions, gave a better yield of the heterocycle **7h**, but the ee decreased to 43% (Table 1, entry 12).[16]

Our results suggest that the bicyclic systems behave similarly to the well-documented desymmetrization of meso cyclohexene oxide using nonracemic lithium amides.[17] An aggregate containing the substrate, the base, and LiCl is supported by the requirement of a nonpolar solvent and an excess of base.[11] As demonstrated for cyclohexene oxide, the deprotonation involves removal of a proton syn to the leaving group.[18] This process corresponds, in the bicyclic substrates, to the removal of a pseudoaxial hydrogen assuming a chair conformation. The requirement for excess Li ions which may act as a Lewis acid suggests that chelation of the remote ethers in association with the bridging oxygen is essential in the activation of the substrate.[19] This postulate is supported by the absence of reactivity for the disilyl ether **2d** which would suppress chelation, and also by the low reactivity of **4a**.[16]

The mechanism of opening of the azaoxabicyclic system involves the BOC group that directs the removal of an equatorial proton α to the nitrogen from a chairlike conformation, as established for the deprotonation of BOC piperidine,[20a,b] to give the equatorially lithiated species followed by the subsequent elimination of the antiperiplanar bridging ether.[20b,c] In this case, the remote ethers were not involved in the process.

In summary, the results reported herein constitute a simple sequence for the enantioselective preparation of functionalized azepines, thiepines, and thiocines.[21]

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Supporting Information Available: Experimental details and characterization for all compounds (12 pages).

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(15) The absolute stereochemistry of **7f** was not determined.

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