Novel Dithia-aza-norbornanes as 'Stiff' Bicyclic Dithiazines

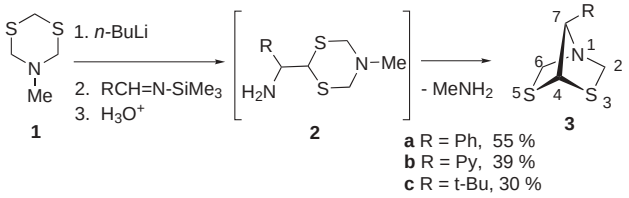
Alexei N. Kurchan, Edmir Wade, Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver, Denver, CO 80208-2436, USA
Fax +1(303)8712254; E-mail: akutatel@du.edu

Received 28 March 2003

Abstract: Addition of lithiated 4,5-dihydro-1,3,5-dithiazines to in situ generated *N*-silylimines in THF produces 2-(α-aminoalkyl)dithiazines, which rearrange into 3,5-dithia-1-azabicyclo[2.2.1]heptanes upon aqueous workup. These novel bicyclic dithiazines can in turn be lithiated at the position 4 and added to carbonyl compounds.

Key words: heterocycles, sulfur, carbanions, nucleophilic additions, diastereoselectivity, desulfurization



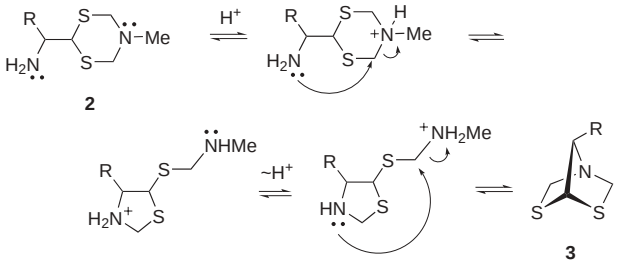
Scheme 1

Reactions of sulfur-stabilized carbanions with various electrophiles have found numerous applications in organic synthesis. Stereochemical aspects of these reactions have been studied in depth and several ingenious approaches that utilize chiral auxiliaries have been implemented. Examples include both external auxiliaries, such as sparteine,[1] and internal auxiliaries, such as menthol esters,[2] chiral dithiane-S-oxides[3] etc.

It was long recognized that sulfur can potentially serve a dual function - it can stabilize the carbanion and, at the same time, it is easily removable when no longer needed.[4] In this Letter we report a novel transformation of 2-aminoalkyl-1,3,5-dithiazines into substituted 3,5-dithia-1-azabicyclo[2.2.1]heptanes, and their subsequent lithiation and reaction with carbonyl compounds. This is an experimentally simple synthetic sequence that, when augmented with desulfurization reactions (e.g. Raney-Ni), offers access to diastereomeric 1,n-diamines or aminoalcohols.

Earlier we found that lithiated dithianes add to in situ generated *N*-silyl imines, furnishing 2-(α-aminoalkyl)-1,3-dithianes.[5] We now report that addition of lithiated dithiazines to *N*-silylated imines produces similar 2-(α-aminoalkyl)-1,3,5-dithiazines **2**, which rearrange into 3,5-dithia-1-azabicyclo[2.2.1]heptanes **3** upon aqueous workup or during chromatography on silica gel, Scheme 1. This transformation gives access to bicyclic dithiazines **3**, in which the auxiliary group R is locked in proximity to the latent anionic center C4.

The most probable mechanism for the conversion of **2** into **3** is a stepwise acid-catalyzed intramolecular nucleophilic substitution shown in Scheme 2. Alternatively, the actual substitution steps 2 and 4 in Scheme 2 may proceed via an S_N1-like mechanism, i.e. formation of a sulfur-stabilized carbocation. Judging by NMR, an increase in acidity accelerates the transformation of the initial reaction mixture. For example, treatment of **2b** with aqueous ammonium chloride/HCl at pH 3 for 15 min and extraction with ethyl acetate gives almost pure **3b**, while a similar work-up at pH 6 gives a mixture of unreacted **2b** and the product **3b** even after 1–2 hours. The caveat is that the overall isolated yield of **3b** at pH 3 is less than 10%, smaller than that of the much slower reaction at near neutral pH.



Scheme 2

Conceivably, this is due to the competing complete hydrolysis of the dithiazine ring at low pH. Under optimal conditions **3a**, the rearranged product of addition to benzaldimine, was obtained in 55% yield by hydrolysis overnight at pH 6.[6] Compounds **3b,c** were obtained similarly by reacting lithiated *N*-methyldithiazine with silylated pyridine-2-carboxaldimine and pivalaldimine respectively. The isolated yield of 7-*tert*-butyl substituted **3b** was low (30%). Generally, we found that increased substitution in the carbonyl component lowered the yield of bicyclic dithiazines. For example, addition of methyldithiazine to *N*-silylated benzophenone imine produced adduct of type **2** that did not rearrange into **3**.

The structure of the bicyclic dithiazines **3** was elucidated by NMR. Compounds **3a**–**c** all lacked the original dithiazine methyl group. In **3a** (Figure 1), six aliphatic protons produce three two-proton spin systems, H_{2x}-H_{2n}, H_{6x}-H_{6n} and H_4-H_7. Additionally, H_{2x}-H_{6x} are weakly W-coupled ($J_{2x\text{-}6x}$ = 1.9 Hz). The geminal coupling constants are $J_{2x\text{-}n}$ = 9.4 Hz and $J_{6x\text{-}n}$ = 9.0 Hz. The benzylic (H_7) and the

Synlett 2003, No. 11, Print: 02 09 2003. Web: 25 08 2003.
Art Id.1437-2096,E;2003,0,11,1731,1733,ftx,en;S04003ST.pdf.
DOI: 10.1055/s-2003-41431

bridgehead (H_4) protons are coupled with $J_{7\text{-}4}$ = 1.2 Hz, which is expected in a bicyclo[2.2.1] framework. The exo-proton H_{2x} is almost half a ppm upfield of H_{6x}. The geometry, optimized at a DFT level (B3LYP/3-21G*), shows that H_{2x} is positioned below the phenyl ring – it is in the shielding part of the aromatic anisotropy cone. The NOE values are in very good agreement with the calculated inter-proton distances (Figure 1). The computed 'horizontal' conformation of the phenyl is supported by the observation that the H_4-H_{ortho} NOE effect (5.4%) is much greater than that of H_7-H_{ortho} (1.2%).

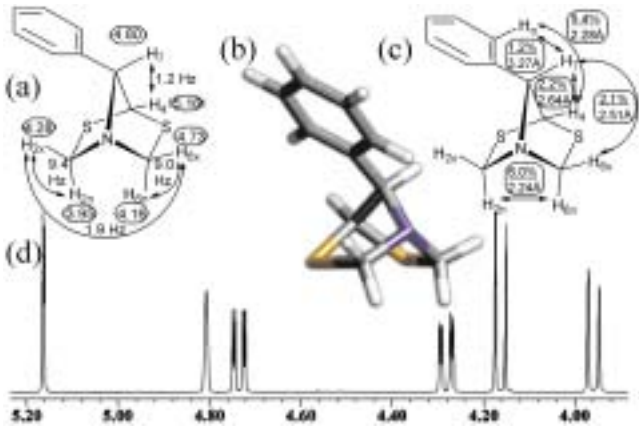
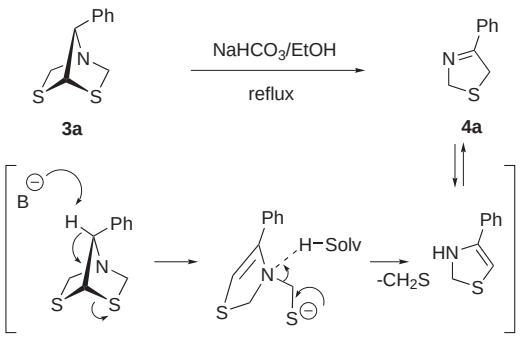


Figure 1 (a) ^{1}H NMR coupling constants and chemical shifts (boxed) for **3a**; (b) B3LYP/3-21G* geometry (c) NOE (%) with DFT inter-proton distances; (d) expansion of the aliphatic region of the spectrum.

Like the parent dithiazines, 3,5-dithia-1-azabicyclo[2.2.1]heptanes are solvolytically unstable in the presence of strong acids. They are relatively stable in basic aprotic solutions but lose one mole of thioformaldehyde and convert into thiazolines upon extended refluxing with bases in protic solutions. For example, refluxing **3a** with sodium bicarbonate in ethanol yields 4-phenyl-2,5-dihydrothiazole **4a** nearly quantitatively.

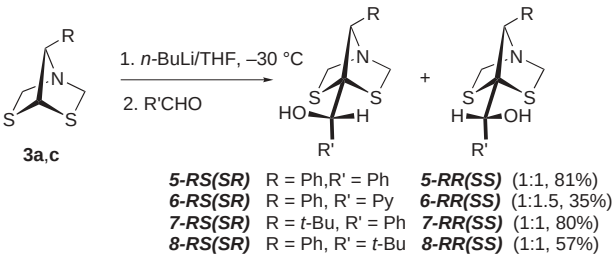
A plausible mechanism for this transformation is shown in Scheme 3. It involves elimination of the benzylic proton and expulsion of thioformaldehyde, which is accelerated by the protic solvent acting as a general acid. Judging by the DFT geometry, the H7-C7-C1-S3 fragment is almost anti-periplanar, 169.4º, which should facilitate the thiolate



Scheme 3

departure. Subsequent enamine-imine tautomerization produces **4a**.

The reaction, however, takes a different path with very strong bases in aprotic solvents. Our further investigation showed that **3a**,**c** are readily deprotonated with butyllithium at C-4, not at the benzylic position. The generated sulfur-stabilized carbanions are reactive toward various electrophiles, including carbonyl compounds. Shown in Scheme 4 are such reactions with aldehydes, producing diastereomers **5**–**8** in moderate to good yields, although with no diastereoselectivity.[7]



5-RS(SR) R = Ph,R' = Ph ***5-RR(SS)*** (1:1, 81%)
6-RS(SR) R = Ph, R' = Py ***6-RR(SS)*** (1:1.5, 35%)
7-RS(SR) R = *t*-Bu, R' = Ph ***7-RR(SS)*** (1:1, 80%)
8-RS(SR) R = Ph, R' = *t*-Bu ***8-RR(SS)*** (1:1, 57%)

Scheme 4

For example, reaction with benzaldehyde produced diastereomers **5**-***RS***(***SR***) and **5**-***RR***(***SS***), which are separated readily by column chromatography, in a 1:1 ratio, Scheme 4. Expansions of the aliphatic region of their NMR spectra are shown in Figure 2. The left-most doublets shown in Figure 2 are benzylic protons. Their splitting is due to spin-spin coupling on the respective protons of the hydroxy groups (not shown in the expansion of aliphatic region). The *RS*(*SR*) diastereomer has its C7-benzylic proton at 4.02 ppm, about 0.9 ppm upfield of the respective benzylic proton in the *RR*(*SS*), 4.92 ppm. Similar large chemical shift differences are also observed in pairs **6** and **8**, which, by analogy, can be used to assign stereochemistry in these diastereomers.

The stereochemical configuration of the diastereomers of **5** was established indirectly, by reductive desulfurization with Raney nickel to the corresponding 1,3-amino-

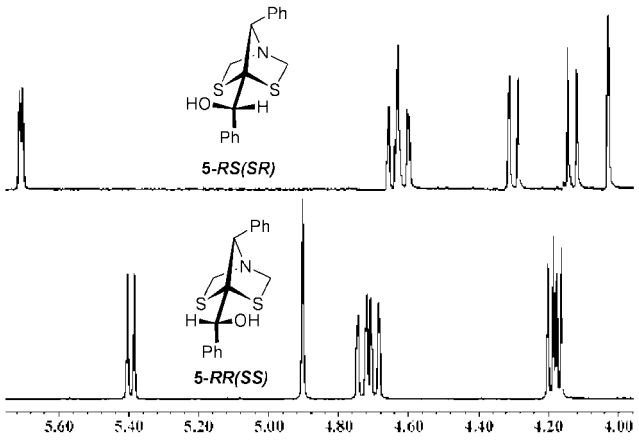
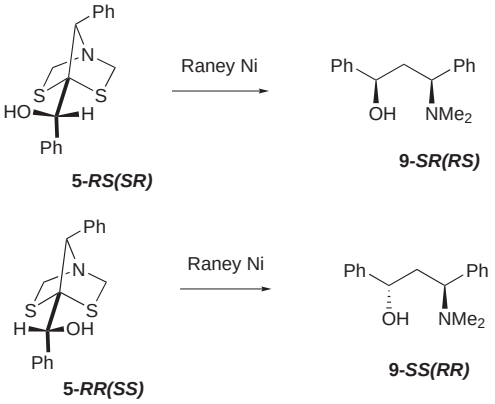


Figure 2 ^{1}H NMR spectrum expansion of the aliphatic region in the diastereomers of **5**.

alcohols, for which the stereochemical assignment was previously described,[8] Scheme 5. Desulfurization with W2 Raney nickel lead to over-reduction, as did the reaction with in situ generated nickel boride.

The best results were achieved with deactivated Raney nickel, treated with acetic acid. In each case we observed only one diastereomer of the amino-alcohol **9** being formed along with by-product 1,3-diphenyl-1-propanol. The reported chemical shifts of the H-C-NMe_2 protons in **9-*SR*(*RS*)** and **9-*SS*(*RR*)** differ by 0.8 ppm making it relatively straightforward to distinguish between the two diastereomers.



Scheme 5

In conclusion, we found that addition of lithiodithiazines to *N*-silylated imines is accompanied by a transformation into novel 3,5-dithia-1-azabicyclo[2.2.1]heptanes, which in turn can be deprotonated at position 4 and added to carbonyl compounds, furnishing diastereomeric adducts. The diastereomers are readily separated by column chromatography, providing easy access to both *RR*(*SS*)- and *RS*(*SR*)-diastereomers. In conjunction with sulfur-removing reactions, for example desulfurization with Raney nickel, this approach can potentially be used to synthesize diastereomeric 1,3-aminoalcohols and related compounds, thus making bicyclic dithiazines **3** a synthon for β-aminoethyl carbanions, $RCH(NMe_2)\text{-}CH_2^-$.

Acknowledgment

Support of this research by the National Science Foundation (Career Award CHE-9876389) is gratefully acknowledged.

References

(1) Kang, J.; Kim, J. I.; Lee, J. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 865.
(2) Ranu, B. C.; Chakraborty, R.; Sarkar, D. C. *Synth. Commun.* **1991**, *21*, 1619.
(3) Allin, S. M.; Page, P. C. B. *Org. Prep. Proced Int.* **1998**, *30*, 145.
(4) For a review see: Vedejs, E. *Adv. Sulfur Chem.* **1994**, *1*, 1.
(5) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 1841.
(6) *Synthesis of **3a** as an example of a general procedure for **3a–c***. (a) *N*-Silyl benzaldimine: A solution of 5.32 g (33 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 100 mL of freshly distilled THF was cooled to 0 °C, and 21.46 mL of *n*-butyllithium (1.6 M solution in hexanes, 34 mmol) was added with stirring under N_2 atmosphere. The reaction mixture was stirred at this temperature for 1.5 h. Next, 3.49 g (33 mmol) of benzaldehyde was slowly added, and the resulting mixture was stirred at 0 °C for 1.5 h; see also: Gyenes, F.; Bergmann, K. E.; Welch, J. T. *J. Org. Chem.* **1998**, *63*, 2824. (b) Lithiated methyldithiazine was prepared by addition of 20.35 mL of 1.6 M *n*-BuLi in hexane (32 mmol) under nitrogen to a solution of 4 g dithiazine (30 mmol) in 100 mL of anhydrous THF at –78 °C. The reaction mixture was stirred for 2 h at –78 °C and a solution of silylated benzaldimine (33 mmol) in 100 mL of anhydrous THF was added dropwise. The solution was stirred at –78 °C for one hour and then allowed to warm to room temperature. The solvent was removed under reduced pressure to give orange oil, to which 150 mL of saturated NH_4Cl was added. The resulting two phase system was stirred for 12 hours at room temperature. The insoluble residue was dissolved in EtOAc, and the water phase was additionally extracted with EtOAc (2 × 50 mL). The organic extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (EtOAc–hexanes, 1:20) resulting in 3.4 g of colorless crystals (54.7% yield). ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.48–7.28 (5 H, m), 5.16 (1 H, d, *J* = 1.4 Hz), 4.80 (1 H, s), 4.73 (1 H, dd, J_1 = 9.0 Hz, J_2 = 1.9 Hz), 4.28 (1 H, dd, J_1 = 9.4 Hz, J_2 = 2.3 Hz), 4.16 (1 H, d, *J* = 9.0 Hz), 3.95(1 H, d, *J* = 9.4 Hz). C^{13} NMR (CDCl3, 100 MHz), δ (ppm) 135.3, 128.5,127.6, 127.2, 82.4, 61.7, 59.5, 56.2. MS (EI) *m/z* (relative intensity) 209 (M^+ 40), 142 (20), 134 (35), 118 (50), 91 (100), 77 (20), 64 (20). Calcd. for $C_{10}H_{11}NS_2$, %: C 57.38, H 5.30; Found, %: C 57.72, H 5.53.
(7) *General procedure.* 2.8 mmol of **3a** or **3c** was dissolved in 30 mL of freshly distilled THF and cooled to –78 °C, under nitrogen atmosphere. Then 2.0 mL (3.2 mmol) of *n*-BuLi 1.6 M solution in hexane was added dropwise. The reaction mixture was stirred for 2 hours at –30 °C and 3.6 mmol of the respective aldehyde in 10 mL of THF was added dropwise. The temperature was maintained at –78 °C for one more hour and then allowed to warm up overnight. The resulting red solution was washed with 50 mL of saturated NH_4Cl, the organic layer separated and the water phase extracted with 30 mL of $CHCl_3$. The organic layers were combined, dried over Na_2SO_4 and the solvent was removed in vacuum to give a yellow oil, which was purified by column chromatography. Additional column separation was required to isolate the diastereomers in a pure state. Diastereomers **5**: (the stereochemistry is assigned based on Raney-Ni desulfurization) **5-*RR*(*SS*)**: ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) 7.86–7.80 (2 H, m), 7.46–7.40 (3 H, m), 7.31–7.20 (3 H, m), 7.16–7.12 (2 H, m), 5.61 (1 H, d, *J* = 3.2 Hz), 4.61 (1 H, d, *J* = 8.8 Hz), 4.59 (1 H, d, *J* = 8.8 Hz), 4.27 (1 H, d, *J* = 8.8 Hz), 4.11 (1 H, d, *J* = 8.8 Hz), 4.02 (1 H, s), 2.45 (1 H, d, *J* = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 140.4, 134.9, 129.7, 129.1, 129.0, 128.7, 128.0, 127.4, 85.9, 83.1, 75.4, 62.2, 60.1 **5-*RS*(*SR*)**: ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) 7.84 (2 H, d, *J* = 7.4 Hz), 7.52–7.36 (7 H, m), 7.33–7.28 (1 H, m), 5.41 (1 H, d, *J* = 8.1 Hz), 4.92 (1 H, s), 4.73 (1 H, d, *J* = 9.5 Hz), 4.70 (1 H, d, *J* = 9.5 Hz), 4.19 (1 H, d, *J* = 9.5 Hz), 4.18 (1 H, d, *J* = 8.8 Hz), 2.87 (1 H, d, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 143.6, 134.6, 129.0, 128.9, 128.8, 128.6, 126.6, 87.2, 83.3, 72.8, 62.1, 61.5.
(8) Liguori, A.; Romeo, G.; Sindona, G.; Uccella, N. *Chem. Ber.* **1988**, *121*, 105.