Ring opening in di[1,2,3]triazolo-[1,3,6]thiadiazepine and -[3,1,5]benzothiadiazepine in reactions with butyllithium

Natalya N. Volkova,[a] Evgeniy V. Tarasov,[a] Mikhail I. Kodess,[b] Wim Dehaen*[c] and Vasiliy A. Bakulev*[a]

[a] *Department of Technology for Organic Synthesis, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3432 745483; e-mail: nvv@htf.ustu.ru*
[b] *Institute of Organic Synthesis, Urals Branch of the Russian Academy of Sciences, 620219 Ekaterinburg, Russian Federation*
[c] *Department of Chemistry, University of Leuven, Heverlee (Leuven), B-3001, Belgium. Fax: +32 016 327990; e-mail: wim.dehaen@chem.kuleuven.ac.be*

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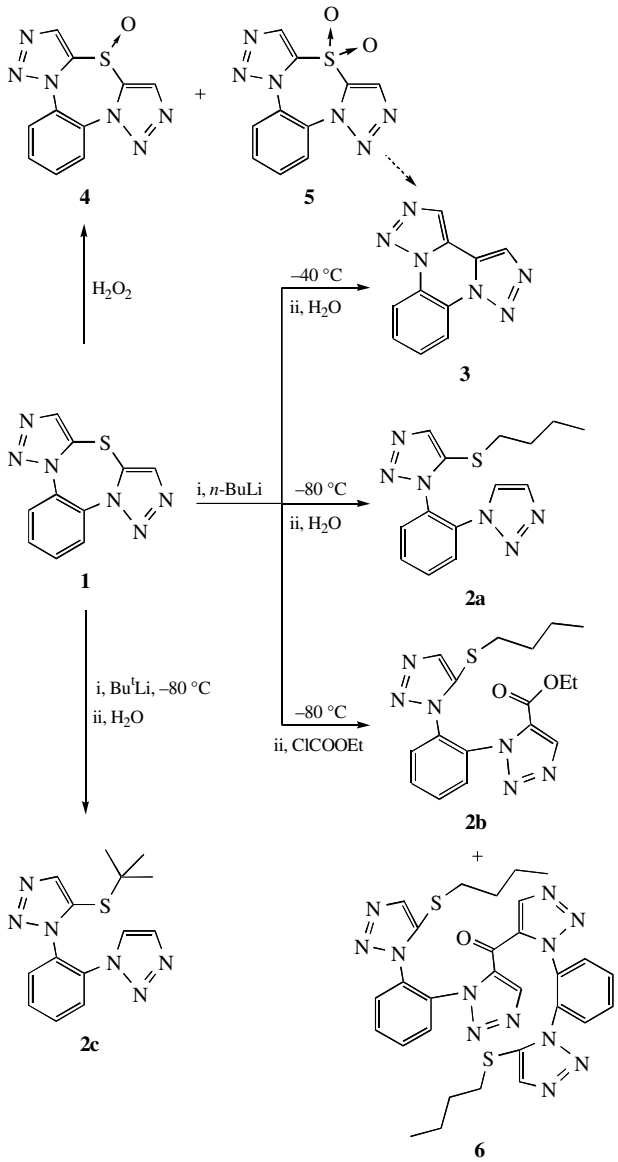
Di[1,2,3]triazolo[1,5-*a*:5′,1′-*d*][3,1,5]benzothiadiazepine treated with butyllithium undergoes ring opening *via* the thiophilic addition of butyllithium at the C–S bond, whereas 9,10-dihydrodi[1,2,3]triazolo[1,5-*b*:5′,1′-*f*][1,3,6]thiadiazepine mainly undergoes lithiation of the methylene group followed by C–N bond cleavage to give 1-vinyltriazolyl sulfide.

Earlier, we reported on the synthesis of a novel fused heterocyclic system containing 1,3,6-thiadiazepine ring **1**.[1] It was of interest to modify the molecule by changing substituents at the triazole rings using organolithium reagents. It is well known that the 1,2,3-triazole ring is easily metallated at the 5-position;[2] however, the metallation occurred at C-4 in the case when the 5-position was occupied.[3,4] The *ortho* phenyl ring with respect to a triazole ring can also be metallated.[5] In this paper, we describe how the treatment of **1** or **7** with *n*-butyllithium leads to the transformation of the heterocyclic system.

When compound **1** (Scheme 1) was treated with *n*-butyllithium in THF at –40 °C, the reaction mixture immediately became dark, and a single product was isolated after addition of water or other quenching agents. The product contained no sulfur, and the structure of quinoxaline **3** was proposed based on mass spectra (the yield was about 20%). The structure of **3** was additionally confirmed by fragmentation analysis in the mass spectra of thiadiazepines with oxidised sulfur. Sulfoxide **4** and sulfone **5** were obtained from compound **1** using hydrogen peroxide in acetic acid and separated by flash chromatography. The mass spectrum of compound **4** or **5** showed a fragmentation pattern almost identical to that of compound **3**, whereas the thiadiazepine ring in compound **1** is rather stable. However, efforts to obtain quinoxaline **3** by thermal elimination of SO (or SO_2, respectively) at 200–280 °C from **4** or **5** were not successful. It is probable that the gas-phase process needs very high temperatures because both sulfone and sulfoxide sublime without any change. At the temperature higher than the temperature of sublimation, the 1,2,3-triazole rings may have thermally cleaved, preventing isolation of **3**. The final confirmation for the structure of quinoxaline **3** was given by ^{1}H and ^{13}C NMR spectra, including ^{1}H coupled ^{13}C NMR and selective irradiation of aromatic protons at δ 7.87 ppm. ^{1}H and ^{13}C signals were assigned using 2D techniques (HETCOR and HMBC).

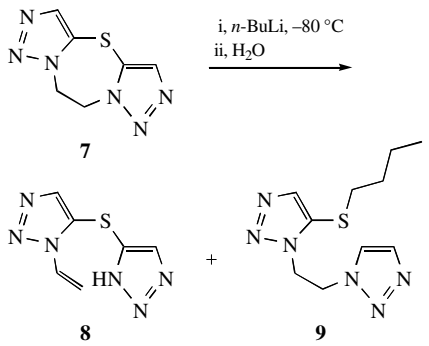
The same quinoxaline **3** was obtained in low yield when *n*-butyllithium was added to **1** at –80 °C followed by warming up the reaction mixture. A colour change was evident at about –40 °C. This experiment showed that at this temperature (–80 °C) the C–S bond of thiadiazepine **1** was cleaved and that as the temperature rose the lithium intermediates started to decompose. Indeed, when the reaction mixture was quenched with water at –80 °C, the only product appeared to be ditriazolylbenzene **2a** bearing a butylsulfanyl group at one of triazole rings.† The same reaction quenched with ethyl chloroformate produced two products, which were identified as ester **2b** and ketone **6**. The formation of ketones from aryllithiums has been described for the use of ethyl chloroformate as a quenching agent.[6] Interestingly, *tert*-butyllithium also acted as a nucleophile in the reaction with **1**, and the same type of product **2c** was obtained.

Thus, butyllithiums cause C–S bond cleavage in the 3,1,5-benzothiadiazepine ring rather than metallation. Although C–S bond cleavage in heterocycles by organolithiums is not widely represented in the literature, a few examples of thiophilic addition at the C-S bond of sulfur-containing five- and six-membered heterocycles has been reported.[7–13] The 5-lithiated triazole obtained in this interaction can be functionalised by treatment with electrophiles. The method gives rise to ditriazolylbenzenes hardly available by other methods.



Scheme 1

Reaction of dihydrodi[1,2,3]triazolo[1,5-*b*:5′,1′-*f*][1,3,6]thiadiazepine **7** with butyllithium proceeded in a different way (Scheme 2). Along with expected compound **9**, which derives from the reaction at the C–S bond, another product was obtained,



7 **8** **9**

Scheme 2

† *Typical experimental procedure.* Butyllithium (2.5 M) in hexane (2 ml, 5.00 mmol) was added dropwise to a stirred solution of thiadiazepine **1** (1 g, 4.13 mmol) in THF (100 ml) at –80 °C under argon. The mixture was stirred for 1 h, and then ethyl chloroformate (0.8 ml, 8.37 mmol) was slowly added. After additional stirring for 1 h, the mixture was quenched with water. The products were extracted with diethyl ether, dried with $MgSO_4$ and concentrated. The residue was separated by flash chromatography to give **2b** (hexane–Et_2O, 5:1; 0.69 g, 44.9%), starting material **1** (Et_2O, 0.08 g, 8%) and ketone **6** ($CHCl_3$, 0.56 g, 21.7%).

2a: yield 81%, pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.83 (t, 3H, Me, *J* 7.0 Hz), 1.22–1.42 (m, 4H, $2CH_2$), 2.54 (t, 2H, SCH_2, *J* 7.3 Hz), 7.27 (d, 1H, C-5′H triaz., *J* 1.1 Hz), 7.58 (dd, 1H, CH, *J* 7.9 and 1.8 Hz), 7.61 (s, 1H, C-4H triaz.), 7.62 (d, 1H, C-4′H triaz., *J* 1.1 Hz), 7.70 (ddd, 1H, CH, *J* 8.0, 8.0 and 1.5 Hz), 7.79 (ddd, 1H, CH, *J* 8.0, 8.0 and 1.7 Hz), 7.93 (dd, 1H, CH, *J* 8.0 and 1.8 Hz, CH). MS, *m*/*z* (%): 300 (M^+, 4), 211 (15), 187 (68), 155 (100), 143 (19), 129 (22), 102 (40).

2b: yield 45%, mp 94 °C. ^{1}H NMR ([$^2H_6$]DMSO + CCl_4, 250 MHz) δ: 0.87 (t, 3H, Me, *J* 6.7 Hz), 1.18 (t, 3H, Me, *J* 7.0 Hz), 1.26–1.50 (m, 4H, $2CH_2$), 2.76 (t, 2H, SCH_2, *J* 7.3 Hz), 4.20 (q, 2H, CH_2, *J* 7.0 Hz), 7.65 (s, 1H, C-4′H triaz.), 7.67–7.88 (m, 4H, CH-arom.), 8.13 (s, 1H, C-4H triaz.). MS, *m*/*z* (%): 372 (M^+, 9), 288 (8), 259 (20), 227 (54), 199 (95), 187 (100), 155 (44), 143 (39), 129 (27), 102 (56), 76 (31).

2c: yield 45%, mp 88–90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.11 (s, 9H, 3Me), 7.22 (d, 1H, C-5′H triaz., *J* 1.1 Hz), 7.57 (dd, 1H, CH, *J* 7.7 and 1.5 Hz), 7.61 (d, 1H, C-4′H triaz., *J* 1.1 Hz), 7.69 (ddd, 1H, CH, *J* 7.7, 7.7 and 1.5 Hz), 7.77 (s, 1H, C-4H triaz.), 7.78 (ddd, 1H, CH, *J* 7.7, 7.7 and 1.5 Hz), 7.92 (dd, 1H, CH, *J* 7.7 and 1.5 Hz). MS, *m*/*z* (%): 300 (M^+, 4), 244 (72), 187 (100), 155 (87), 102 (39), 57 (87).

3: yield 20%, mp 220 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz): 7.85–7.88 (m, 2H, 2CH-*meta*), 8.62–8.65 (m, 2H, 2CH-*ortho*), 8.69 (s, 2H, 2CH-triaz.). ^{13}C NMR ([$^2H_6$]DMSO, 100 MHz) δ: 116.94 (dm, C-*ortho*, *J* 168.6 Hz), 123.14 (ddd, C-*ipso*, *J* 9.2, 6.4 and 2.1 Hz), 123.53 (d, C5-triaz., *J* 15.3 Hz), 129.41 (d, C4-triaz., *J* 201.8 Hz), 129.47 (ddd, C-*meta*, *J* 166.3, 8.2 and 0.8 Hz). MS, *m*/*z* (%): 210 (M^+, 42), 182 (24), 154 (25), 128 (34), 103 (27), 76 (100).

6: yield 22%, mp 149–151 °C. ^{1}H NMR ([$^2H_6$]DMSO + CCl_4, 250 MHz) δ: 0.85 (t, 6H, Me, *J* 6.9 Hz), 1.29–1.42 (m, 8H, $2CH_2$), 2.72 (t, 4H, SCH_2, *J* 7.1 Hz), 7.63 (s, 2H, C-4′H triaz.), 7.60–7.84 (m, 4H, CH-arom.), 8.19 (s, 1H, C-4H triaz.). MS, *m*/*z* (%): 626 (M^+, 1), 598 (3), 542 (10), 308 (26), 295 (27), 187 (100), 155 (68), 143 (31), 129 (47), 102 (62), 90 (37), 57 (77).

Oxidation. Thiadiazepine **1** (0.5 g, 2.07 mmol) was refluxed in acetic acid with 2 ml of 30% H_2O_2 overnight. The reaction mixture was evaporated *in vacuo*, and two products were separated using flash chromatography (eluent: CH_2Cl_2–hexane, 1:3 for sulfone **5** and CH_2Cl_2 for sulfoxide **4**).

4: yield 40%, sublimation at 228 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz) δ: 7.89–7.97 (m, 2H, 2CH-arom.), 8.19–8.28 (m, 2H, 2CH-arom.), 8.70 (s, 2H, 2CH-triaz.). MS, *m*/*z* (%): 258 (M^+, 10), 174 (12), 154 (32), 129 (27), 103 (45), 76 (100).

5: yield 40%, sublimation at 200–202 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.86–7.89 (m, 2H, 2CH-arom.), 8.17–8.20 (m, 2H, 2CH-arom.), 8.38 (s, 2H, 2CH-triaz.). MS, *m*/*z* (%): 275 (MH^+, 100), 211 (10), 183 (32), 155 (34), 128 (10), 103 (2).

8: yield 56%, mp 72 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.33 (dd, 1H, CH, *J* 8.8 and 1.1 Hz), 6.20 (dd, 1H, CH, *J* 15.3 and 1.1 Hz), 7.47 (dd, 1H, NCH, *J* 15.3 and 8.8 Hz), 7.65 (s, 1H, CH triaz.), 7.85 (s, 1H, CH triaz.). MS, *m*/*z* (%): 195 (MH^+, 100).

9: yield 22%, colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, Me, *J* 6.9 Hz), 1.34–1.48 (m, 4H, $2CH_2$), 2.58 (t, 2H, SCH_2, *J* 7.3 Hz), 4.87 (dd, 2H, CH_2, *J* 6.6 and 4.4 Hz), 5.05 (dd, 2H, CH_2, *J* 6.6 and 4.4 Hz), 7.24 (d, 1H, C-5′H triaz., *J* 0.7 Hz), 7.62 (d, 1H, C-4′H triaz., *J* 0.7 Hz), 7.64 (s, 1H, C-4H triaz.).

which was identified as 5-(1*H*-1,2,3-triazol-5-ylsulfanyl)-1-vinyl-1*H*-1,2,3-triazole **8**. We propose that this reaction proceeds *via* metalation of the methylene group followed by ring opening, analogously to the decomposition of ethers.[14]

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