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A new approach to densely functionalised azepines and dihydroazepines

Nina A. Nedolya,*[a] Ol'ga A. Tarasova,[a] Alexander I. Albanov,[a] Ol'ga G. Volostnykh,[a] Lambert Brandsma[b] and Boris A. Trofimov[a]

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 41 9346; e-mail: nina@irioch.irk.ru*
[b] *Utrecht University, 3584 CH Utrecht, The Netherlands. E-mail: l.brandsma@wxs.nl*

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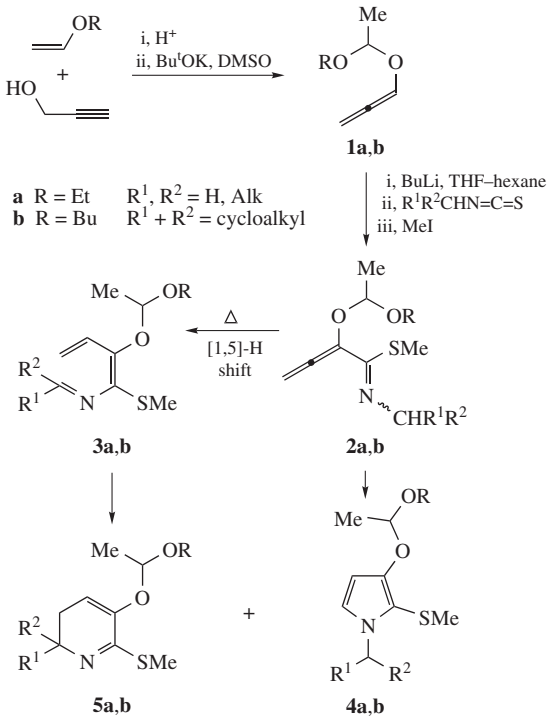
The easy transformation of 2-(1-alkoxyethoxy)-*N*-(1-methylethylidene)-1-(methylsulfanyl)-1,3-butadien-1-amines (2-aza-1,3,5-trienes) into 3-(1-alkoxyethoxy)-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines and 6-(1-alkoxyethoxy)-2-methyl-3*H*-azepines has been found to proceed under the action of Bu^{t}OK in THF–DMSO or THF; the mild acidic hydrolysis of 4,5-dihydro-3*H*-azepines gives hydroxy derivatives.

Previously, we found that allenylimidothioates $R^1R^2C{=}C{=}C(R^3){-}C(SR^4){=}NR^5$ (1-aza-1,3,4-trienes) are generated in nearly quantitative yields from readily available lithiated allenes or alkynes and isothiocyanates.[1] These reactive intermediates can undergo various inter-[2] and intramolecular[3–11] transformations including [1,5]-H and [1,3]-SR sigmatropic rearrangements, [2 + 2]-cycloadditions, [1,5]-cyclizations and 6π-electrocyclizations to form 2-aza-1,3,5-trienes and four-, five- and six-membered carbo- and azaheterocycles such as cyclobutanes,[2] cyclobutenes,[3] pyrroles,[4] cyclobuta[1,2-*a*]pyrroles,[5] 2,3-dihydropyridines,[5(c),6] 5,6-dihydro-2(1*H*)-pyridinones,[7] 5,6-dihydro-3(4*H*)-pyridinones,[8] pyridines,[9] 2(1*H*)-pyridinethiones[10] and quinolines.[5(c),11] Applying this methodology to protected allenol **1**, which is readily available from propargyl alcohol and vinyl ethers[1(a)] (Scheme 1), gives previously inaccessible allenic **2** and butadienic **3** imines and products of their cyclizations – alkylsulfanyl substituted pyrroles,[12] 2,3-dihydropyridines,[8,9(b)] 5,6-dihydro-3(4*H*)-pyridinone[8] and pyridines[9(b)] bearing very reactive and biologically important acetal, hydroxy or keto groups.

Recently, we found that 2-aza-1,3,5-triene, $H_2C{=}CH{-}C(OMe){=}C(SMe){-}N{=}CMe_2$, product of [1,5]-H shift in the corresponding 1-aza-1,3,4-triene derived from allenic ether and isothiocyanate, undergoes an unprecedented transformation to 3-methoxy-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepine and 6-methoxy-2-methyl-3*H*-azepine with a ratio of ~3:1 to ~1:1 depending on reaction conditions.[13]

The availability of the allenic acetals $H_2C{=}C{=}CHOCH(Me)OR$ (R = Alk) and the importance of seven-membered azaheterocycles in biology and medicine,[14] along with known biological activity of acetal structures,[15] prompt us to employ the allenic acetals as building blocks to assemble functionalised azepines. The synthesis of azepines, which incorporate the reactive acetal function that is available for further transformations, could have significant impact on the design of drugs and new rare functionalised azepines including their hydroxy derivatives.

Here, we report the first methodology for the construction of both azacycloheptadienyl and azacycloheptatrienyl acetals, namely, 3-(1-alkoxyethoxy)-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines **6** and 6-(1-alkoxyethoxy)-2-methyl-3*H*-azepines **7**, in a single step based on the treatment of 2-aza-1,3,5-trienes having acetal moiety **3**, which were prepared from lithiated allenic acetals **1** and isopropyl isothiocyanate according



Scheme 1

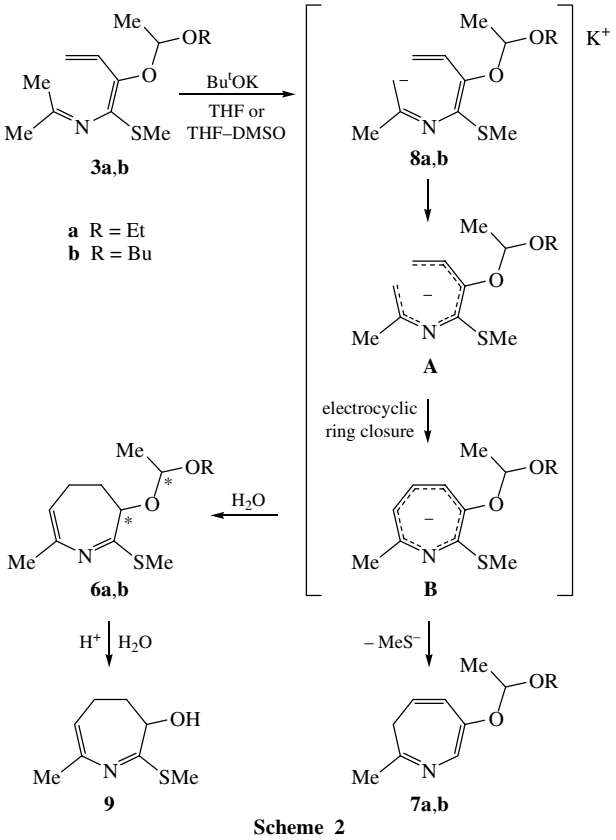
to a published procedure[1(a)] ($R^1 = R^2 = Me$, Scheme 1) with potassium *tert*-butoxide (Scheme 2).†

The reaction was carried out in dry THF–DMSO (4.3–4.6:1, by volume) at –30 °C with a slight excess (1.1–1.2 equiv.) of Bu^{t}OK for 30 min. After aqueous work-up, compounds **6a** and **7a** were obtained in 89% yield. 4,5-Dihydro-3*H*-azepine **6a** (as a mixture of diastereomers) was the major reaction product (88% in the mixture, NMR); the **6a**:**7a** ratio is ~12.5:1. About 5% of pyrrole **4a** (R = Et, $R^1 = R^2 = Me$) as a by-product of 2-aza-1,3,5-triene **3a** synthesis (Scheme 1) was identified by NMR spectroscopy in the mixture of products. Flash chromatography on neutral Al_2O_3 gives compounds **6a** and **7a** in 59 and 6% isolated yields, respectively.

The reaction of 2-aza-1,3,5-triene **3a** with Bu^{t}OK in dry THF (in the absence of DMSO) at 0 °C for 10 min provided products, **6a**, **7a** and **4a** in nearly the same ratio (NMR) and

~82% total yield. Compounds **6a** and **7a** were isolated in 42 and 7% yields, respectively, by flash chromatography on Al_2O_3.

Similar results are attained when 2-aza-1,3,5-triene **3b**, derived from earlier unknown 1-(1-butoxyethoxy)allene (isomerised adduct of propargyl alcohol and *n*-butyl vinyl ether), isopropyl isothiocyanate and methyl iodide, is treated with potassium *tert*-butoxide (1.2 equiv.) under the above conditions (THF–DMSO, –30 °C, 30 min). Flash chromatography on Al_2O_3 gives 4,5-dihydro-3*H*-azepine **6b** and 3*H*-azepine **7b** in 59 and 5% isolated yields, respectively. Pyrrole **4b** (R = Bu, $R^1 = R^2 = Me$, Scheme 1) was also detected (~5%) by NMR spectroscopy in crude products.



Scheme 2

Tentative mechanistic routes leading to 4,5-dihydro-3*H*-azepines **6** and 3*H*-azepines **7** are depicted in Scheme 2. The formation of an azepine ring likely involves the deprotonation of a methyl group from the azomethine moiety (N=CMe_2) of compounds **3** followed by the isomerization of initially formed carbanions **8** and the [1,7]-electrocyclization of isomerised anions **A** resulted in the formation of azacycloheptadienyl anionic species **B** (also *via* hydrogen shifts after the initial ring closure reaction). The final protonation of cyclic anions **B** gives (directly or after hydrogen shift) 4,5-dihydro-3*H*-azepines **6**. The unprecedented elimination of the sulfide anion from anionic intermediate **B** under the reaction conditions affords 3*H*-azepine **7**. The possible formation of the latter as a product of further elimination of MeSH from 4,5-dihydro-3*H*-azepine **6** (or its isomers) is excluded. This is evidenced by the stability of the ratio between compounds **6** and **7** upon storage or chromatographic isolation as well as from the absence of the peak of azepine **7** in the chromatogram of 4,5-dihydro-3*H*-azepine **6**.

The careful treatment of an ethereal solution of 4,5-dihydro-3*H*-azepines **6** with ~3% aqueous hydrochloric acid (room temperature, 12 min) followed by neutralization with KOH afforded 4,5-dihydro-3*H*-azepin-3-ol **9** as colourless needles (after recrystallization from light petroleum) in ~62% yield (Scheme 2).

The structures of the products were assigned using ^{1}H, ^{13}Cjmod, homo- and heteronuclear 2D (COSY-^{1}H×^{1}H, HSQC-^{1}H×^{13}C, HMBC-^{1}H×^{13}C, HMBC-^{1}H×^{15}N) NMR and IR spectroscopy. 4,5-Dihydro-3*H*-azepines **6a**,**b** containing two asymmetric carbon atoms were obtained as diastereoisomeric mixtures. Their ^{1}H and ^{13}C NMR spectra show two sets of lines.

In conclusion, we reported the first synthesis of new acetal- or hydroxy-functionalised 4,5-dihydro-3*H*-azepines and 3*H*-azepines

† All the reactions (other than the hydrolysis of compounds **6**) were performed under anhydrous conditions and in an argon atmosphere. For all reactions at low temperatures, a cooling bath with liquid nitrogen was used. The IR spectra were obtained on Bruker IFS-25 and Vertex-70 spectrometers. The ^{1}H (400.13 MHz), ^{13}C (100.61 MHz) and 2D NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers with HMDS as internal standard. ^{13}C resonance assignments were done with the use of 2D HSQC and HMBC heteronuclear (^{1}H×^{13}C) correlation methods.

*3-(1-Ethoxyethoxy)-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepine* **6a** *and 6-(1-ethoxyethoxy)-2-methyl-3*H*-azepine* **7a**. To a stirred solution of crude 2-aza-1,3,5-triene **3a** (8.31 g, 33 mmol, in admixture with ~2% of pyrrole **4a**) in THF (40 ml), cooled to –65 °C, a mixture of DMSO (11 ml) and THF (11 ml) and subsequently Bu^{t}OK (4.03 g, 36 mmol) were added. Reaction mixture was warmed to –30 °C and stirred for 30 min. The solution was cooled to –60 °C and water (150 ml) was added. The layers were separated and five extractions with diethyl ether were carried out. Combined organic solutions were washed with water (three times) and dried over $MgSO_4$. After removal of the solvents under a reduced pressure (~1 Torr at ~60 °C), the remaining brown mobile liquid (7.29 g, 89%), a mixture of 4,5-dihydro-3*H*-azepine **6a** (88%), 3*H*-azepine **7a** (7%) and pyrrole **4a** (5%), was separated into the components by flash column chromatography on neutral Al_2O_3 [eluent: light petroleum for compounds **4a** and **6a** or light petroleum–Et_2O (1:1) for compound **7a**].

*4,5-Dihydro-3*H*-azepine* **6a** (as a mixture of diastereomers in a ratio of ~1:2): yield 59% (4.66 g), light yellow mobile liquid, n_D^{26} 1.4908. IR (thin layer, ν/cm^{-1}): 477, 526, 539, 587, 711, 728, 786, 799, 842, 871, 896, 915, 932, 948, 980, 1007, 1029, 1065, 1086, 1126, 1142, 1178 (OCHO), 1244, 1313, 1329, 1378, 1392, 1442, 1481, 1576, 1632 (C=N, C=C), 2861, 2887, 2924, 2945, 2976, 3031, 3132. GCMS (EI, 70 eV), *m*/*z*: 243 [M]$^{+\cdot}$.

For major diastereomer of **6a**: ^{1}H NMR ($CDCl_3$) δ: 5.20 (ddq, 1H, 6-CH=, ^3J 7.84 Hz, ^3J 5.35 Hz), 4.67 (q, 1H, OCHO), 4.53 (dd, 1H, 3-CH, ^3J 10.70 Hz, ^3J 8.00 Hz), 3.50, 3.52 (2m, 2H, OCH_2, AB qq, ^2J 9.40 Hz), 2.38, 2.16 (2m, 2H, 5-CH_2), 2.29 (s, 3H, SMe), 1.90, 1.77 (2m, 2H, 4-CH_2), 1.86 (d, 3H, 7-Me, ^4J 1.30 Hz), 1.35 (d, 3H, CH*Me*, ^3J 5.41 Hz), 1.16 (t, 3H, CH_2*Me*, ^3J 7.05 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.82 (C=N), 147.22 (7-C=), 110.02 (6-CH=), 99.52 (OCHO), 75.60 (3-CH), 58.99 (OCH_2), 43.31 (5-CH_2), 22.08 (7-Me), 21.14 (4-CH_2), 19.56 (CH*Me*), 15.44 (CH_2*Me*), 12.02 (SMe).

For minor diastereomer of **6a**: ^{1}H NMR ($CDCl_3$) δ: 5.19 (ddq, 1H, 6-CH=, ^3J 7.84 Hz, ^3J 5.35 Hz), 4.78 (q, 1H, OCHO), 4.52 (dd, 1H, 3-CH, ^3J 10.70 Hz, ^3J 8.00 Hz), 3.74, 3.53 (2m, 2H, OCH_2, AB qq, ^2J 9.60 Hz, ^3J 7.08 Hz), 2.38, 2.16 (2m, 2H, 5-CH_2), 2.29 (s, 3H, SMe), 1.90, 1.77 (2m, 2H, 4-CH_2), 1.85 (d, 3H, 7-Me, ^4J 1.30 Hz), 1.28 (d, 3H, CH*Me*, ^3J 5.41 Hz), 1.16 (t, 3H, CH_2*Me*, ^3J 7.05 Hz). ^{13}C NMR ($CDCl_3$) δ: 175.24 (C=N), 147.32 (7-C=), 109.86 (6-CH=), 99.16 (OCHO), 72.61 (3-CH), 62.28 (OCH_2), 43.58 (5-CH_2), 22.01 (7-Me), 21.14 (4-CH_2), 19.61 (CH*Me*), 15.15 (CH_2*Me*), 12.14 (SMe).

7a: yield 6% (0.38 g), yellow-orange liquid, n_D^{23} 1.5070. IR (film, ν/cm^{-1}): 439, 516, 528, 574, 630, 648, 680, 712, 729, 759, 825, 858, 887, 901, 932, 950, 990, 1047, 1077, 1093, 1111, 1129, 1170, 1204 (OCHO), 1241, 1289, 1340, 1382, 1413, 1425, 1443, 1459, 1526, 1617, 1655 (C=N, C=C), 2875, 2932, 2975. ^{1}H NMR ($CDCl_3$) δ: 7.18 (br. s, 1H, 7-CH=), 6.25 [dd, 1H, 5-CH=, $^4J_{H(5)–H(7)}$ 1.5 Hz], 5.32 [dt, 1H, 4-CH=, $^3J_{H(4)–H(5)}$ 9.05 Hz, $J_{H(4)–H(3)}$ 7.09 Hz], 5.06 (q, 1H, OCHO), 3.77, 3.50 (dq, 2H, OCH_2), 2.62, 2.33 (m, 2H, 3-CH_2), 2.13 (s, 3H, 2-Me), 1.38 (d, 3H, CH*Me*, *J* 5.38 Hz), 1.16 (t, 3H, CH_2*Me*, *J* 6.58 Hz). ^{13}C NMR ($CDCl_3$) δ: 147.62 (C=N), 146.70 (6-C=), 128.92 (7-CH=), 125.34 (5-CH=), 116.81 (4-CH=), 101.24 (OCHO), 62.02 (OCH_2), 37.72 (3-CH_2), 26.32 (2-Me), 20.52 (CH*Me*), 15.10 (CH_2*Me*). GCMS (EI, 70 eV), *m*/*z*: 195 [M]$^{+\cdot}$.

by easy proton abstraction from 2-aza-1,3,5-trienic systems prepared from inexpensive and readily available starting materials: propargylic alcohol, vinyl ethers and isothiocyanates. The methodology described for the construction of seven-membered azaheterocycles secures the rapid access to a variety of polyfunctionalised azepines and their partially hydrogenated derivatives using appropriate 2-aza-1,3,5-trienes, which are readily available from metallated allenes or alkynes and isothiocyanates.[1]

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Online Supplementary Materials

Supplementary data associated with this article (experimental procedures and characterization data for compounds **3a**,**b**, **6b**, **7b** and **9**) can be found in the electronic version at doi:10.1016/j.mencom.2008.05.018.

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