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A new approach to densely functionalised azepines and dihydroazepines

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Experimental

All the reactions (with the exception of 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 a 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 a 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.

2-(1-Ethoxyethoxy)-N-*(1-methylethylidene)-1-(methylsulfanyl)-1,3-butadien-1-amine* **3a**. To a stirred solution of Bu^{n}Li (51.2 mmol) in hexane (~32 ml) and THF (55 ml), cooled to −100 °C, 1-(1-ethoxyethoxy)allene **1a** (6.4 g, 50 mmol) in admixture with THF (5 ml) was added in one portion, after which the temperature of the solution was allowed to rise to −60 °C. After stirring for an additional 10 min at ~ −70÷−60 °C, the solution was cooled to −90 °C and a mixture of isopropyl isothiocyanate (5.04 g, 50 mmol) and THF (5 ml) was added in one portion. The temperature of the reaction mixture was allowed to rise to −35÷−30 °C, which level was maintained for an additional 20 min. The solution was cooled to −80 °C and methyl iodide (13.5 g, 95 mmol, excess) was then added in one portion, after which the temperature was allowed to rise to 20 °C for 30 min. After cooling to −80 °C, an aqueous solution of NH_4Cl (60 ml) was added with vigorous stirring. The layers were separated and four extractions from the aqueous layer with small portions of diethyl ether were carried out. Combined organic solutions were washed with water and dried over $MgSO_4$. The solvents were removed under a reduced pressure (on rotary evaporator, then on oil pump at ~1 mm Hg), while keeping the bath temperature below 17 °C. The remaining light-brown mobile liquid (12.41 g, 100%) consisted of methyl 2-(1-ethoxyethoxy)-*N*-isopropyl-2,3-butadienimidothioate **2a** (R^1 = R^2 = Me) (54%, as a mixture of *syn*- and *anti*-isomers in a ratio of ~37:63), 2-aza-1,3,5-triene **3a** (44%) and 3-(1-ethoxyethoxy)-1-isopropyl-2-(methylsulfanyl)-1*H*-pyrrole **4a** (2%) by NMR. The isomerization of 1-aza-1,3,4-triene **2a** into 2-aza-1,3,5-triene **3a** (*via* [1,5]-H shift) was completed by storage at rt for 4 h.

^{1}H NMR ($CDCl_3$) δ: 6.01 (dd, 1H, CH=), 5.29 (dd, 1H, CH_2=, *trans*, $^3J_{trans}$ 17.20 Hz), 5.17 (q, 1H, OCHO), 4.91 (dd, 1H, CH_2=, *cis*, $^3J_{cis}$ 11.25 Hz, $^2J_{gem}$ 1.80 Hz), 3.90, 3.60 (dq, 2H, OCH_2, ^2J 9.24 Hz), 2.18 (s, 3H, SMe), 2.05, 1.88 (2s, 6H, CMe_2), 1.45 (d, 3H, CH*Me*, ^3J 5.22 Hz), 1.17 (t, 3H, CH_2*Me*, ^3J 7.09 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.05 (C=N), 133.75 (OC=), 132.98 (SC=), 126.51 (CH=), 108.93 (CH_2=), 99.96 (OCHO), 62.65 (OCH_2), 25.98 (Me), 19.75 (Me), 19.35 (Me), 13.64 (Me), 11.30 (SMe).

2-(1-Butoxyethoxy)-N-(1-methylethylidene)-1-(methylsulfanyl)-1,3-butadien-1-amine **3b** was prepared similarly to compound **3a**. Yield ~100% (11.25 g), brownish liquid. ^{1}H NMR ($CDCl_3$) δ: 6.01 (dd, 1H, CH=), 5.30 (dd, 1H, CH_2=, *trans*, $^3J_{trans}$ 17.37 Hz), 5.16 (q, 1H, OCHO), 4.91 (dd, 1H, CH_2=, *cis*, $^3J_{cis}$ 11.00 Hz, $^2J_{gem}$ 1.72 Hz), 3.86, 3.51 (dt, 2H, OCH_2, ^2J 9.50 Hz, ^3J 6.60 Hz), 2.18 (s, 3H, SMe), 2.05, 1.88 (2s, 6H, CMe_2), 1.52 (m, 2H, β-CH_2), 1.44 (d, 3H, CH*Me*, ^3J 5.40 Hz), 1.36 (m, 2H, γ-CH_2), 0.89 (t, 3H, $(CH_2)_3$*Me*, ^3J 7.60 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.75 (C=N), 135.59 (OC=), 134.61 (SC=), 128.28 (CH=), 110.75 (CH_2=), 102.00 (OCHO), 68.97 (OCH_2), 32.04 (β-CH_2), 27.72, 21.49 (C*Me*$_2$)), 21.03 (γ-CH_2), 19.07 (CH*Me*), 13.78 [$(CH_2)_3$*Me*], 13.05 (SMe).

The reaction using **3b** (8.13 g, 30 mmol, in admixture with ~4% of pyrrole **4b**), Bu^{t}OK (4.03 g, 36 mmol), THF (51 ml) and DMSO (11 ml) led to a mixture (by NMR) of 4,5-dihydro-3*H*-azepine **6b** (87.5%), 3*H*-azepine **7b** (7.5%) and pyrrole **4b** (5%); 7.29 g of crude products.

3-(1-Butoxyethoxy)-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3H-azepine **6b** (as a mixture of diastereomers in ratio of ~1:2): purified by flash column chromatography (Al_2O_3, eluent – light petroleum: Et_2O, 10:1), yield 59.2% (4.62 g), light yellow mobile liquid, $n_D^{20.5}$ 1.4848. IR (film, ν/cm^{-1}): 576, 532, 588, 648, 668, 680, 711, 730, 785, 799, 862, 878, 895, 921, 952, 981, 1006, 1030, 1068, 1089, 1141, 1178, 1244, 1313, 1330, 1380, 1391, 1449, 1577, 1632, 2872, 2923, 2957, 2984, 3132. ^{1}H NMR ($CDCl_3$) δ: 5.20 (m, 1H, 6-CH=), 4.76, 4.67 (q, 1H, OCHO), 4.54, 4.52 (dd, 1H, 3-CH, $J_{ax\text{-}ax}$ 10.70 Hz, $J_{ax\text{-}eq}$ 7.96 Hz), 3.65, 3.39 (dt, 2H, OCH_2, minor, $^2J_{AB}$ 9.50 Hz, ^3J 6.57 Hz), 3.46, 3.42 (dt, 2H, OCH_2, major, $^2J_{AB}$ 9.22 Hz, ^3J 6.50 Hz), 2.39, 2.14 (2 m, 2H, 5-CH_2), 2.29 (s, 3H, SMe), 1.91, 1.76 (2 m, 2H, 4-CH_2), 1.85 (nm, 3H, 7-Me), 1.51 (m, 2H, β-CH_2), 1.35 (m, 2H, γ-CH_2), 1.34, 1.28 (d, 3H, CH*Me*, ^3J 5.29 Hz), 0.90, 0.89 [t, 3H, $(CH_2)_3$*Me*, ^3J 7.30 Hz]. ^{13}C NMR ($CDCl_3$) δ: 175.20, 174.80 (C=N), 147.24, 147.13 (7-C=), 109.94, 109.78 (6-CH=), 99.46, 99.16 (OCHO), 75.34, 72.62 (3-CH), 66.36, 63.38 (OCH_2), 43.34, 43.18 (5-CH_2), 31.93, 31.72 (β-CH_2), 21.97, 21.91 (7-Me), 21.04, 20.99 (4-CH_2), 19.46, 19.41 (CH*Me*), 19.30, 19.28 (γ-CH_2), 13.83, 13.81 [$(CH_2)_3$*Me*], 12.04, 11.92 (SMe). GCMS (EI, 70 eV), *m/z*: 271 $[M]^{+\cdot}$.

6-(1-Butoxyethoxy)-2-methyl-3H-azepine **7b**: purified by flash column chromatography (Al_2O_3, eluent – light petroleum: Et_2O, 1:1), yield 4.7% (0.31 g), brown viscous liquid, $n_D^{20.5}$ 1.4998. IR (film, ν/cm^{-1}): 442, 515, 574, 630, 647, 680, 732, 757, 825, 847, 886, 919, 955, 989, 999, 1030, 1063, 1129, 1170, 1205, 1288, 1341, 1381, 1414, 1429, 1455, 1527, 1616, 1657, 2873, 2930, 2960. ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, 1H, 7-CH=), 6.25 (dd, 1H, 5-CH=, $^4J_{H(5)–H(7)}$ 2.32 Hz), 5.32 (dt, 1H, 4-CH=, $^3J_{H(4)–H(5)}$ 9.29 Hz, $^3J_{H(4)–CH_2}$ 7.09 Hz), 5.06 (q, 1H, OCHO), 3.70, 3.43 (2 dt, 2H, OCH_2, $^2J_{AB}$ 9.29 Hz, ^3J 6.60 Hz), 2.64, 2.36 (m, 2H, 3-CH_2), 2.13 (s, 3H, 2-Me), 1.54 (m, 2H, β-CH_2), 1.38 (d, 3H, CH*Me*, ^3J 5.38 Hz), 1.34 (m, 2H, γ-CH_2), 0.89 [t, 3H, $(CH_2)_3$*Me*, ^3J 7.34 Hz]. ^{13}C NMR ($CDCl_3$) δ: 147.78 (C=N), 146.90 (6-C=), 128.84 (7-CH=), 125.44 (5-CH=), 116.90 (4-CH=), 101.44 (OCHO), 66.40 (OCH_2), 37.78 (3-CH_2), 31.80 (β-CH_2), 26.41 (2-Me), 20.51 (CH*Me*), 19.36 (γ-CH_2), 13.88 [$(CH_2)_3$*Me*]. GCMS (EI, 70 eV), *m/z*: 223 $[M]^{+\cdot}$.

7-Methyl-2-(methylsulfanyl)-4,5-dihydro-3H-azepin-3-ol **9**. The solution of 4,5-dihydro-3*H*-azepine **6a** (2.66 g, 10.9 mmol) in Et_2O (40 ml) was vigorously shaken with hydrochloric acid (3.2 ml of 30% HCl, ~26 mmol, 30 ml of water) for ~12 min. After separation of the layers, followed by neutralization of the acidic layer with KOH (10% aqueous solution), the product was extracted with diethyl ether (5×20 ml), combined ethereal solutions were washed with water (2 times) and dried over $MgSO_4$. After concentration of the organic solution under a reduced pressure, the 4,5-dihydro-3*H*-azepin-3-ol **9** remained as a solid. Yield 62.5% (1.17 g) after recrystallization from light petroleum, colourless needles, mp 85–88 °C. IR (KBr, ν/cm^{-1}): 527, 587, 786, 826, 887, 911, 969, 1007, 1034, 1044, 1079, 1093, 1133, 1175, 1237, 1280, 1304, 1331, 1370, 1411, 1443, 1562, 1636 (C=N, C=C), 2858, 2916, 2945, 2975, 3028, 3273, 3393 (OH). ^{1}H NMR (DMSO-d_6) δ: 5.64 (d, 1H, OH), 5.20 (m, 1H, 6-CH=), 4.32 (m, 1H, 3-CH), 2.34 (m, 1H, 5-CH_2), 2.19 (s, 3H, SMe), 1.94 (m, 1H, 5-CH_2), 1.78 (s, 3H, 7-Me), 1.73 (m, 2H, 4-CH_2). ^{13}C jmod NMR (DMSO-d_6) δ: 177.92 (C=N), 146.42 (7-C=), 109.81 (6-CH=), 71.04 (3-CH), 44.10 (5-CH_2), 22.02 (7-Me), 21.03 (4-CH_2), 11.58 (SMe). 2D ^{1}H×^{15}N HMBC NMR (DMSO-d_6, $MeNO_2$), δ_N: –78.30 (=N−C−Me). GCMS (EI, 70 eV), *m/z*: 171 $[M]^{+\cdot}$. Found (%): C, 56.97; H, 7.36; N, 8.20; S, 18.53. Calc. for $C_8H_{13}NOS$ (%): C, 56.10; H, 7.65; N, 8.18; S, 18.72.

Hydrolysis of 4,5-dihydro-3*H*-azepine **6b** gave compound **9** in 62% yield.