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LETTERS TO THE EDITOR

Arylsubstituted 3*H*-Azepines and 4,5-Dihydro-3*H*-Azepines from Propargylbenzene and Isothiocyanates

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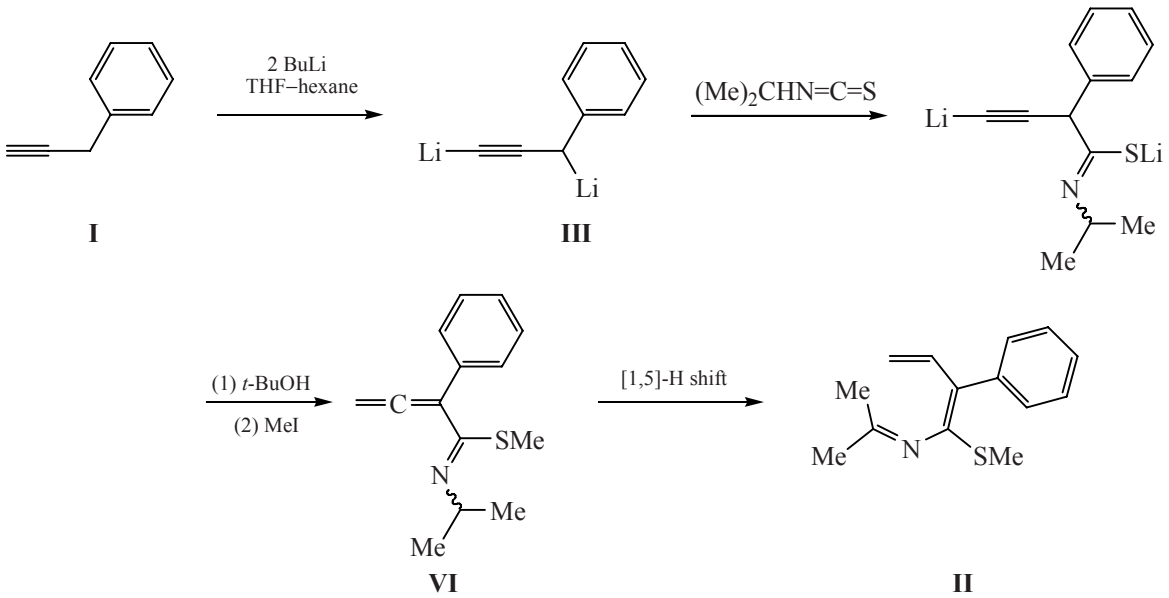
Earlier we have shown that the adducts of the dilithiated propargylbenzene (**I**) with isothiocyanates (lithium allenylimidothioates, their S-alkylated derivatives and the products of sigmatropic rearrangements of the latter including 2-aza-1,3,5-trienes) are universal precursors of such important four-, five-, and six-membered carbo- and heterocycles as cyclobutenimines [1–5], cyclobutenones [6], thietanimines [1, 2, 4, 7], thiophenamines [1, 2], 2,3-dihydropyridines and quinolines [5], whose formation proceeds via various (as a rule, earlier unknown) thermally controlled intramolecular rearrangements and cyclizations.

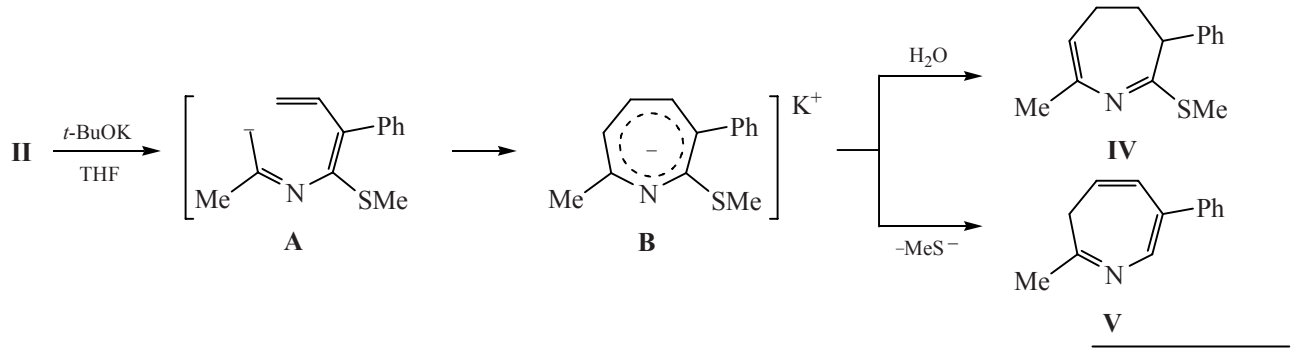
In continuation of these studies, we have found that 2-aza-1,3,5-triene (**II**) prepared from 1,3-dilithiopropargylbenzene (**III**), isopropyl isothiocyanate and methyl iodide (Scheme 1), under the action of equimolar amount of *t*-BuOK (THF, 15°C, ~30 min) is smoothly converted into the earlier unknown 7-methyl-2-(methylsulfanyl)-3-phenyl-4,5-dihydro-3*H*-azepine (**IV**) and 2-methyl-6-phenyl-3*H*-azepine (**V**) in ~1:1 ratio (^{1}H NMR data) (Scheme 2). Total yield of products **IV** and **V** was >74% (after flash chromatography on silica, conditions nonoptimized).

Scheme 1.



I **III** **VI** **II**

Scheme 2.



The last step of the reaction (Scheme 2) suggests mild deprotonation of 2-aza-1,3,5-triene (**II**) on one of the methyl groups of the azomethine fragment and fast 1,7-electrocyclization of the formed intermediate **A** into azacycloheptadienyl anion **B** with subsequent protonation leading to 4,5-dihydro-3*H*-azepine (**IV**), and competitive elimination of methylsulfide anion leading to 3*H*-azepine (**V**).

Methoxy-substituted 4,5-dihydro-3*H*-azepine and 3*H*-azepine we recently synthesized from α-lithiated methoxyallene and isopropyl isothiocyanate [8]. However, the results described here cannot be considered predictable since the thermally induced intramolecular transformations of methoxy- and phenyl-substituted precursors of 2-aza-1,3,5-trienes, S-lithiated and S-alkylated allenylimidothioates (1-aza-1,3,4-trienes) prepared accordingly from methoxyallene and propargyl-benzene **I**, follow principally different routes. Methoxy derivatives always give five-membered aza- and thiaheterocycles (pyrroles and thiophenes) [9–13], whereas in the latter case, as mentioned above, four-membered carbo- and heterocycles (cyclobutenes and thietanes) [1–7] and only in a few cases thiophenes are formed [1, 2]. Such a change of the reaction course caused by a simple change of methoxy group for phenyl group was absolutely unexpected. That is why it was interesting and important to know how will behave the phenyl-substituted 2-aza-1,3,5-triene in a superbasic medium.

The example given demonstrates that the reaction of deprotonation of 2-aza-1,3,5-trienes readily generated from the available propargylarenes [14] and *sec*-alkyl or cycloalkyl isothiocyanates can serve a basis for expedient synthetic approach to aryl-substituted 3*H*-azepines and 4,5-dihydro-3*H*-azepines that are of considerable theoretical [15, 16], synthetic [17–20], and practical [21–25] interest.

***N*-(1-Methylethylidene)-1-(methylsulfanyl)-2-phenyl-1,3-butadien-1-amine (II).** To the solution of 3.48 g of propargylbenzene **I** in 70 ml THF 61.6 mmol of BuLi solution in 38.5 ml of hexane was added at –100°C during ~1 min. The reaction mixture was stirred for 10 min at 10–12°C, then cooled to –90°C, and the solution of 3.03 g of isopropyl isothiocyanate in 5 ml of THF was added in one portion. After stirring for 10 min at −45 to −40°C, first the mixture of 2.4 g of *t*-BuOH and ~2 ml of Et-$_2$O was added (at –55 to –40°C), and then 12 g of MeI (at ~–50°C). The reaction mixture was stirred for ~2 h at room temperature, then saturated aqueous solution of NH_4Cl was added at –30°C while vigorous stirring. Reaction products were extracted with Et_2O (2×40 ml), the combined organic fraction was washed with water (3 times), dried over $MgSO_4$, organic solution was concentrated under a reduced pressure (temperature of the bath <30°C). The residue [6.64 g (95.8%), dark oil] containing according to the ^{1}H NMR spectrum >90% of **methyl-*N*-isopropyl-2-phenyl-2,3-butadienimidothioate (VI)** (1-aza-1,3,4-triene, mixture of the *syn*- and *anti*-isomers), was purified by flash chromatography (~2 cm layer of SiO_2, eluent is petroleum ether). Yield 5.11 g (74%). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.05 d (6H, CH*Me*$_2$, ^3J 6.21), 2.37 s (3H, SMe), 3.75 heptet (1H, C*H*Me$_2$, ^3J 6.21), 5.25 s (2H, CH_2=), 7.20–7.38 m (5H, Ph) (major isomer); 1.25 d (6H, CH*Me*$_2$, ^3J 6.23), 2.33 s (3H, SMe), 3.95 heptet (1H, C*H*Me$_2$, ^3J 6.23), 5.33 s (2H, CH_2=), 7.20–7.38 m (5H, Ph) (minor isomer; ratio 69:31).

1-Aza-1,3,4-triene **VI** was heated at ~80–85°C (1–4 mm Hg) for 35 min to practically quantitative isomerization into 2-aza-1,3,5-triene **II**; light brownish liquid, content of the main compound ~95% (^{1}H NMR data), n_D^{22} 1.6064. ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.97 s (3H, SMe), 1.99 s and 2.23 s (6H, CMe_2), 4.46

d.d (1H, CH_2=, *cis*, J^{cis} 10.64, J^{gem} 1.71), 4.81 d.d (1H, CH_2=, *trans*, J^{trans} 17.24, J^{gem} 1.71), 6.41 d.d (1H, CH=, J^{trans} 17.24, J^{cis} 10.64), 7.20–7.35 m (5H, Ph). ^{13}C NMR ($CDCl_3$), δ_C, ppm: 13.79 (SMe), 21.24 (Me), 27.50 (Me), 112.23 (CH_2=), 121.35 (2-C), 126.96 (*p*-CH, Ph), 128.10 (*m*-CH, Ph), 130.67 (*o*-CH, Ph), 133.60 (CH=), 137.63 (*ipso*-C, Ph), 142.07 (1-C), 172.39 (N=C).

Reaction of 2-aza-1,3,5-triene (II) with potassium *tert*-butoxide. Synthesis of compounds (IV) and (V). To the solution of 3.57 g of 2-aza-1,3,5-triene **II** in 18 ml of THF the solution of 1.67 g of *t*-BuOK in 15 ml of THF was added by pipette at –80°C. After warming to –12°C (after 8 min) the mixture was warmed to 15°C, stirred for 30 min, cooled to –80°C, and treated with saturated aqueous solution of NH_4Cl. Reaction products were extracted with diethyl ether (3×35 ml), combined organic fraction was washed with water (4×10 ml), dried over $MgSO_4$, the solvent removed under a reduced pressure (temperature of the bath ~40°C). The residue, 3.3 g (92.4%) of viscous dark-brown liquid, was purified by flash chromatography (SiO_2, eluent was Et_2O–petroleum ether, 1:3). 2.65 g (74.2%) of viscous dark-brown liquid was obtained in which 4,5-dihydro-3*H*-azepine **IV** and 3*H*-azepine **V** in the ratio ~1:1 were identified by NMR and mass spectrometry. Compounds **IV** and **V** were isolated in the individual state using column chromatography (SiO_2, eluents benzene and $CHCl_3$). For confirmation of their structure and full assignment of the signals in the NMR spectra 2D COSY-45, 2D HSQC and 2D HMBC NMR experiments were performed.

7-Methyl-2-(methylsulfanyl)-3-phenyl-4,5-dihydro-3*H*-azepine (IV). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.93 d [3H, Me, ^4J(Me–H_6) 1.34], 1.96 m (2H, 5-CH_2), 2.23 s (3H, SMe), 2.30 d.d.d.d and 2. 64 d.d.d.d [2H, 4-CH_2, ^2J(H_4–$H_{4'}$) 13.08, ^3J(H_4–$H_{5'}$) 12.30, ^3J(H_4–H_3) 6.60, ^3J(H_4–H_5) 2.93], 4.08 d.d [1H, 3-CH, ^3J(H_3–$H_{4'}$) 11.62, ^3J(H_3–H_4) 6.60], 5.29 d.d.q [1H, 6-CH, ^3J(H_6–$H_{5'}$) 7.58, ^3J(H_6–H_5) 5.38, ^4J(Me–H_6) 1.34], 7.26–7.31 m (5H, Ph). ^{13}C NMR (*j* mod) ($CDCl_3$), δ_C, ppm: 13.34 (SMe), 22.56 (Me), 23.57 (4-CH_2), 40.37 (5-CH_2), 50.88 (3-CH), 110.41 (6-CH), 127.41 (*p*-CH, Ph), 127.86 (*o*-CH, Ph), 129.68 (*m*-CH, Ph), 138.71 (7-C), 147.11 (*ipso*-C, Ph), 173.14 (N=C). Mass spectrum, *m/z* ($I_{rel.}$, %): 231 (16) $[M]^{+\cdot}$, 216 (27), 203 (12), 184 (100), 182 (24), 147 (20), 143 (10), 141 (23), 129 (19), 128 (17), 117 (37), 115 (50).

2-Methyl-6-phenyl-3*H*-azepine (V). ^{1}H NMR ($CDCl_3$), 50°C[1], δ, ppm (*J*, Hz): 2.18 d [3H, Me, ^5J(Me–C=N–CH) 0.73], 2.54 br.s (2H, 3-CH_2), 5.43 d.t.d [1H, 4-CH, ^3J(H_4–H_5) 9.05, ^3J(H_4–CH_2) 6.97, ^5J(H_4–H_7) 0.61], 6.43 d.d [1H, 5-CH, ^3J(H_5–H_4) 9.05, ^4J(H_5–H_7) 1.83], 7.28 m (1H, *p*-CH, Ph), 7.36 m (2H, *m*-CH, Ph), 7.44 m (2H, *o*-CH, Ph), 7.64 d.d.q [1H, 7-CH, ^4J(H_7–H_5) 1.83, ^5J(H_7–H_4) 0.61]. ^{13}C NMR (*j* mod) ($CDCl_3$), δ_C, ppm: 26.30 (Me), 38.42 (3-CH_2), 116.41 (4-CH), 127.08 (5-CH), 127.52 (*o*-CH, Ph), 128.21 (*p*-CH, Ph), 128.47 (*m*-CH, Ph), 129.14 (6-C), 138.14 (7-CH), 140.57 (*ipso*-C, Ph), 149.92 (N=C). Mass spectrum, *m/z* ($I_{rel.}$, %): 183 (100) $[M]^{+\cdot}$, 182 (74), 181 (9), 168 (36), 167 (20), 142 (24), 141 (93), 139 (9), 116 (7), 115 (53), 102 (6), 91 (16), 89 (9), 83 (7), 77 (10), 76 (8), 70 (20), 65 (9), 63 (16), 57 (10), 51 (17), 50 (8), 39 (21).

^{1}H and ^{13}C NMR spectra were registered on a Bruker DPX-400 spectrometer [working frequencies 400.13 (^{1}H) and 100.61 MHz (^{13}C)] from ~5–10% solutions in $CDCl_3$, internal reference HMDS. Electron impact mass spectra (70 eV) were obtained on a Shimadzu GCMS-QP5050A instrument.

All operations were performed under an argon atmosphere. Mixtures were cooled by liquid nitrogen. THF was purified by powdered KOH (~50 g l^{-1}) and distillation over $LiAlH_4$ in the presence of benzophenone under an argon atmosphere. Propargylbenzene **I** and isopropyl isothiocyanate were prepared by procedures described in [14] and [9], respectively. Commercial butyllithium (~1.6 M solution in hexane) and other reagents and solvents were used.

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