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SHORT COMMUNICATIONS

Reactions of Lithiated Allenes with Isothiocyanates: First Example of Deprotonation of 2-Aza-1,3,5-trienes. Synthesis of 6-Methoxy-2-methyl-3*H*-azepine and 3-Methoxy-7-methyl-2-methylsulfanyl-4,5-dihydro-3*H*-azepine

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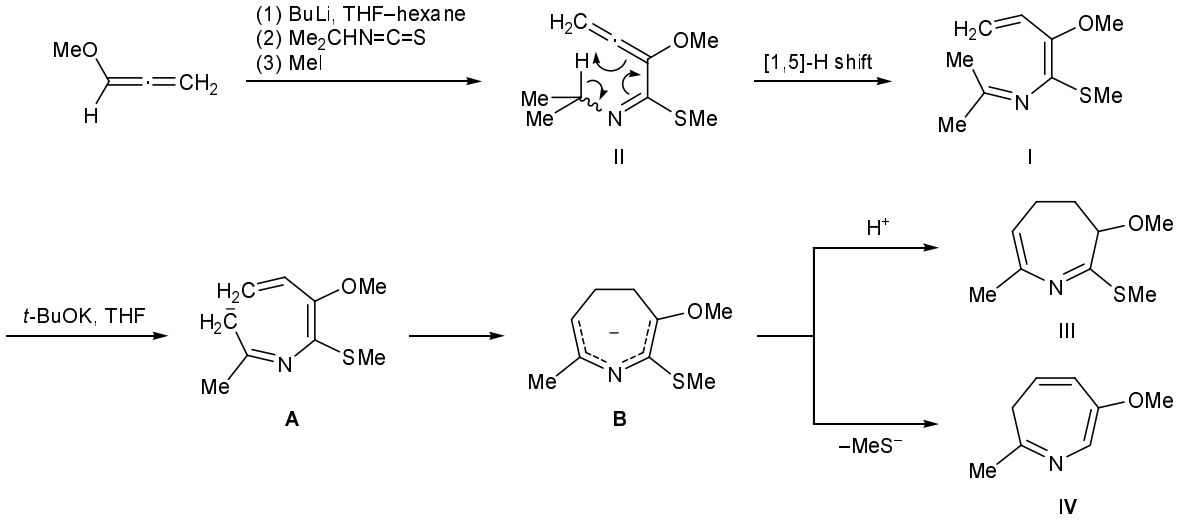
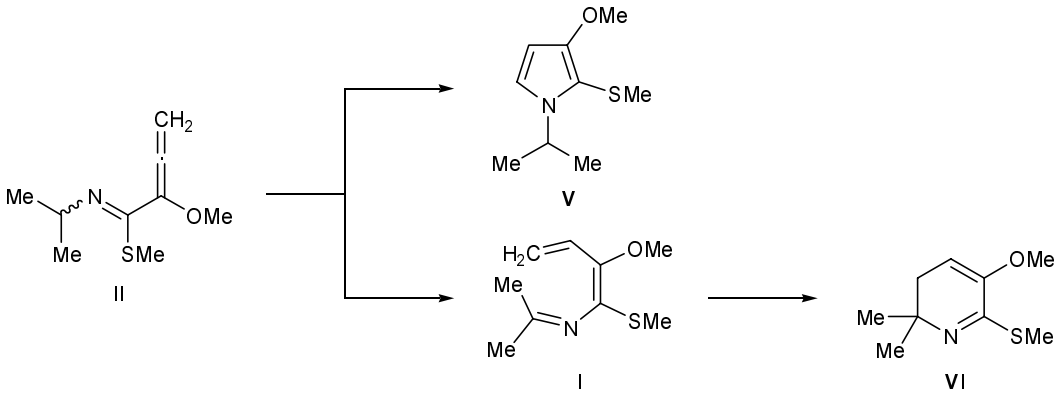
Recently discovered [1] reactions of lithiated allenes with isothiocyanates have been considered so far to underlie a novel approach to one-pot synthesis of five- and six-membered nitrogen- and sulfur-containing heterocycles belonging to new families of C-alkylsulfanyl-substituted pyrroles, 2-azabicyclo[3.2.0]hept-2-enes, 2,3-dihydropyridines, pyridines, quinolines, 2-aminothiophenes, and 2,5-dihydrothiophen-2-imines [2]. While continuing studies in this line, we were the first to find out that 2-aza-1,3,5-triene **I**, which is readily available via [1,5]-sigmatropic rearrangement of 1-aza-1,3,4-triene **II** (C-alkylated adduct of 1-lithio-1-methoxyallene and isopropyl isothiocyanate [1]) is converted in almost quantitative yield to hitherto unknown 3-methoxy-7-methyl-2-methylsulfanyl-4,5-dihydro-3*H*-azepine (**III**) and 6-methoxy-2-methyl-3*H*-azepine (**IV**) by the action of 1–1.3 equiv of *t*-BuOK (Scheme 1). The ratio of compounds **III** and **IV** depends on the reaction conditions. In THF at ~0°C (10 min), the major product was 4,5-dihydro-3*H*-azepine **III** (ratio **III**:**IV** ≈ 3:1, overall yield ~71%), while in the system THF–DMSO (4:1, by volume; –30 to –25°C, 30 min) compounds **III** and **IV** were formed in comparable amounts with the same overall yield. As by-products we identified pyrrole **V** and (in some cases) 2,3-dihydropyridine **VI**, which were formed via

Scheme 1.



Scheme 2.



concurrent intramolecular [1,5]-cyclization of 1-aza-1,3,4-triene **II** and [1,6]-electrocyclization of 2-aza-1,3,5-triene **I**, respectively [1, 2] (Scheme 2). Their yield ranged from 5 to 15%, depending on the conditions of isomerization of intermediate **II**.

Presumably, deprotonation of one methyl group in the azomethine fragment of 2-aza-1,3,5-triene **I** by the action of potassium *tert*-butoxide gives carbanion **A** which undergoes spontaneous [1,7]-electrocyclization to produce azacycloheptadienyl anion **B**. Proton addition to **B** leads to 4,5-dihydro-3*H*-azepine **III**, while concurrent elimination of methylsulfanyl anion yields 3*H*-azepine **IV** (Scheme 1).

We have developed a simple and convenient procedure for the isolation of individual products **III** and **IV** from the reaction mixture with the use of dilute hydrochloric acid solutions. The product structure was confirmed by the NMR (^{1}H, ^{13}C, ^{13}C JMOD, COSY, HSQC, HMBC) and mass spectra.

It should be emphasized that we have found no published data on metalation of 2-aza-1,3,5-trienes, electrocyclization of 2-aza-1,3,5-trienyl anions, and synthesis of seven-membered aza heterocycles from allenes and isothiocyanates. Klotgen and Wurthwein [3] reported on the synthesis of some 1*H*-azepine derivatives, namely 1-acyl-2,3-dihydro-1*H*-azepines and 1-substituted 4,5-dihydro-1*H*-azepines from lithiated 1-phenyl-7-*p*-tolyl-2-azaheptatriene $PhCH_2N{=}CHCH{=}CHCH{=}CHTol\text{-}p$ and *N*-allyl-*N*-(3-phenyl- or 3-thienylprop-2-enylidene)amine $CH_2{=}CHCH_2N{=}CHCH{=}CHAr$, respectively. These reactions were carried out in three steps: (1) lithiation at the activated azamethylene group (lithium diisopropylamide, –78°C, 50 min); (2) [1,7]-electrocyclization (40°C, 3 h); and (3) N-alkylation or N-acylation (–40°C, 20 min; room temperature, 16 h) [3].

Thus even our first experiments showed that azapolyene systems readily generated from accessible polyunsaturated carbanions and heterocumulenes [1, 2] are promising as a new source of azacycloheptadienes and -trienes which constitute new families of 3*H*-azepine derivatives. The general character of the described approach was confirmed by other successful reactions of this type.

2-Methoxy-*N*-(1-methylethylidene)-1-methylsulfanylbuta-1,3-dien-1-amine (2-aza-1,3,5-triene) (I). Methoxyallene, 6 g (85.7 mmol), was quickly added to a solution of 64 mmol of BuLi in 40 ml of hexane and 70 ml of THF, cooled to –100°C. The mixture was stirred for 10 min at –70 to –60°C, cooled again to –100°C, and 5.05 g (50 mmol) of isopropyl isothiocyanate was added in one portion. The mixture warmed up to –30°C and was stirred for 10–15 min at –35 to –30°C. It was then cooled to –80°C, 16 g (112.7 mmol) of methyl iodide was added in one portion, the mixture was stirred for 20 min at room temperature and cooled to –80°C, and ~100 ml of a saturated aqueous solution of ammonium chloride was added under vigorous stirring. The organic phase was separated, the aqueous phase was treated with diethyl ether (3×50 ml), and the extracts were combined with the organic phase, washed with water (3×30 ml), dried over $MgSO_4$, and evaporated on a rotary evaporator. The residue was 9.06 g (98%) of a light brown mobile liquid which, according to the ^{1}H NMR data, was a mixture of two isomeric methyl *N*-isopropyl-2-methoxybuta-2,3-dienimidothioates (1-aza-1,3,4-trienes **II**). ^{1}H NMR spectrum, δ, ppm: 5.70 s and 5.63 s (2H, CH_2=), 3.94 br.m (1H, NCH), 3.48 s and 3.42 s (3H, OMe), 2.39 s and 2.25 s (3H, SMe), 1.17 d and 1.09 d (6H, CH**Me**$_2$).

Heating of 1-aza-1,3,4-triene **II** at ~65–67°C for a short time (~10–15 min) afforded 2-aza-1,3,5-triene **I**

as a brown liquid containing ~10% of 1-isopropyl-3-methoxy-2-methylsulfanylpyrrole (**V**) [1]. ^{1}H NMR spectrum of **I**, δ, ppm: 5.91 d.d (1H, CH=, J_{trans} = 17.24, J_{cis} = 10.76 Hz), 5.18 d.d (1H, *trans*-CH_2=, J_{trans} = 17.24, ^2J = 1.96 Hz), 4.90 d.d (1H, *cis*-CH_2=), 3.63 s (3H, OMe), 2.17 s (3H, Me), 2.07 s (3H, SMe), 1.89 s (3H, Me). ^{13}C NMR spectrum of **I**, δ_C, ppm: 173.68 (N=C), 137.82 (C^2), 134.00 (CH=), 126.24 (C^1), 109.42 (CH_2=), 58.15 (OMe), 27.53 (Me), 20.92 (Me), 12.50 (SMe).

Reaction of 2-aza-1,3,5-triene (I) with potassium *tert*-butoxide. *a*. A suspension of 5.04 g (45.1 mmol) of potassium *tert*-butoxide in 10 ml of THF was added through a pipette to a mixture of 8.3 g (44.8 mmol) of 2-aza-1,3,5-triene **I** (containing an impurity of pyrrole **V**) and 5 ml of THF, cooled to –80°C. When the mixture warmed up to 0°C (in several minutes), it was stirred for 10 min and cooled to –80°C, and 80 ml of a saturated aqueous solution of ammonium chloride was added. The organic phase was separated, the aqueous phase was extracted with diethyl ether (3× 40 ml), the extracts were combined with the organic phase, washed with three portions of water, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was 7.84 g of a dark brown viscous liquid which, according to the NMR and mass spectra, contained pyrrole **V**, 4,5-dihydro-3*H*-azepine **III**, 3*H*-azepine **IV**, and 2,3-dihydropyridine **VI**, the ratio **III**:**IV**:**VI** being ~7:1.8:1. Vacuum distillation of that mixture gave azeotrope mixtures differing in the component ratios [fraction *I*: bp 70–75°C (2–3 mm), n_D^{20} = 1.4668; fraction *II*: bp 77–81°C (2–3 mm), n_D^{20} = 1.4679; fraction *III*: bp 92–94°C (2–3 mm)] and was accompanied by considerable losses (up to 60%) as a result of tarring and decomposition (most probably, of seven-membered aza heterocycles). Individual compounds were isolated by column and/or thin-layer chromatography on Silicagel 60 (0.063–0.200 mm) using benzene and chloroform as eluents.

b. A mixture of 5 ml DMSO and 5 ml of THF and 2.18 g (19.5 mmol) of powdered potassium *tert*-butoxide were added in succession under vigorous stirring to a solution of 3 g (16.2 mmol) of 2-aza-1,3,5-triene **I** (containing ~5–7% of pyrrole **V**) in 20 ml of THF, cooled to –65°C. The mixture was allowed to warm up to –30°C (over a period of 4 min), stirred for 30 min at –30 to –25°C, and cooled to –50°C, and 80 ml of ~1.5% hydrochloric acid was added (the temperature rose to 0°C). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (3× 40 ml). The extracts were combined with the organic phase, washed with several small portions of water, and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain 2.15 g of a crude material which contained (according to the NMR and mass spectra) 4,5-dihydro-3*H*-azepine **III** (major product) and pyrrole **V**. The aqueous phase was neutralized with an aqueous solution of potassium hydroxide and extracted with diethyl ether (3×35 ml). The extracts were combined and dried over $MgSO_4$, and the solvent was removed on a rotary evaporator. The residue was 0.84 g (37.8%) of 3*H*-azepine **IV** which was additionally purified by flash chromatography on aluminum oxide using petroleum ether and chloroform as eluents. The mixture containing compounds **III** and **V** was dissolved in 100 ml of diethyl ether, and the solution was treated with 40 ml of ~8% hydrochloric acid. From the acid aqueous phase we isolated 1 g (33.4%) of 4,5-dihydro-3*H*-azepine **III**, and pyrrole **V** was identified in the organic phase.

3-Methoxy-7-methyl-2-methylsulfanyl-4,5-dihydro-3*H*-azepine (III). Light yellow liquid. ^{1}H NMR spectrum, δ, ppm: 5.18 d.d.q (1H, 6-H, $^3J_{6,5'}$ = 7.70, $^3J_{6,5}$ = 5.26, $^4J_{6,Me}$ = 1.25 Hz), 4.00 d.d (1H, 3-H, $^3J_{3,4'}$ = 10.42, $^3J_{3,4}$ = 7.76 Hz), 3.36 s (3H, OMe), 2.47 m and 2.07 m (2H, C^4H_2), 2.30 s (3H, SMe), 1.90 m and 1.75 m (2H, C^5CH_2), 1.86 d.d (3H, Me, $^5J_{Me,5}$ = 1.70, $^4J_{Me,6}$ = 1.30 Hz). ^{13}C NMR spectrum (JMOD), δ_C, ppm: 174.99 (N=C), 147.39 (C^7), 109.99 (C^6), 82.07 (C^3), 59.17 (OMe), 42.74 (C^4), 22.06 (Me), 20.99 (C^5), 11.86 (SMe). Mass spectrum, *m*/*z* (I_{rel}, %): 185 $[M]^+$ (44), 170 (49), 153 (15), 112 (100), 97 (18), 96 (22), 55 (27), 53 (46), 39 (30). Found, %: C 58.49; H 8.34; N 7.33; S 17.02. $C_9H_{15}NOS$. Calculated, %: C 58.34; H 8.16; N 7.56; S 17.31.

6-Methoxy-2-methyl-3*H*-azepine (IV). Light yellow liquid. ^{1}H NMR spectrum, δ, ppm: 6.90 d (1H, 7-H, $^4J_{7,5}$ = 2.45 Hz), 6.16 d.d (1H, 5-H, $^3J_{5,4}$ = 9.29, $^4J_{5,7}$ = 2.45 Hz), 5.30 d.t (1H, 4-H, $^3J_{4,5}$ = 9.29, $^3J_{4,3}$ = 7.10 Hz), 3.65 s (3H, OMe), 2.48 m (2H, C^3H_2), 2.10 s (3H, Me). ^{13}C NMR spectrum (JMOD), δ_C, ppm: 150.36 (N=C), 147.82 (C^6), 124.58 (C^4), 121.14 (C^5), 118.00 (C^7), 56.02 (OMe), 37.23 (C^3), 25.55 (Me). Mass spectrum, *m*/*z* (I_{rel}, %): 137 $[M]^+$ (87), 136 (23), 122 (100), 107 (23), 94 (32), 81 (24), 67 (25), 66 (24), 65 (35), 53 (92), 43 (23), 42 (23), 41 (44), 39 (79). Found, %: C 70.19; H 7.94; N 10.31. $C_8H_{11}NO$. Calculated, %: C 70.04; H 8.08; N 10.21.

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-250 (250.13 and 62.9 MHz, respectively) and Bruker DPX-400 spectrometers (400.13 and 100.61 MHz, respectively) from ~5–10% solutions in

$CDCl_3$ using HMDS as internal reference. The mass spectra were obtained on a GCMS-QP5050A system.

All operations were performed under argon. Tetrahydrofuran was purified by treatment with mechanically dispersed KOH (~50 g/l), followed by distillation over $LiAlH_4$ in the presence of benzophenone under argon. Butyllithium (a ~1.6 M solution in hexane) was prepared from metallic lithium and butyl chloride. Methoxyallene and isopropyl isothiocyanate were synthesized according to the procedures described in [4] and [1], respectively. The other reagents and solvents used in this work were commercial products. Liquid nitrogen was used as cooling agent.

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