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Structural reorganization of (allyl-, benzyl-, and propargylsulfanyl) -substituted 2-aza-1,3,5-trienes in *t*-BuOK/THF/DMSO: access to rare functionalized 2-thiazolines

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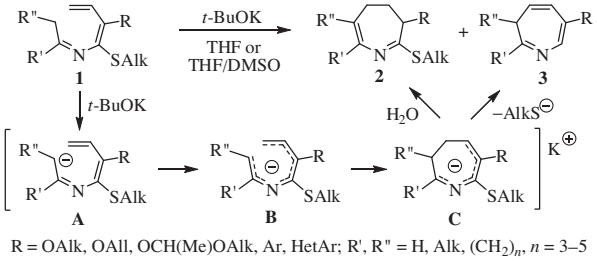
ABSTRACT

Treatment of (allyl-, benzyl-, and propargylsulfanyl)-substituted 2-aza-1,3,5-trienes, which are readily accessible from lithiated methoxyallene, isopropyl isothiocyanate, and allyl, benzyl, or propargyl bromide, respectively, with *t*-BuOK in THF/DMSO resulted in the unexpected formation of 2-thiazoline derivatives along with seven-membered azaheterocycles [in the case of (allyl- and benzylsulfanyl)-substituted 2-aza-1,3,5-trienes]. An unprecedented structural reorganization of the azatrienes into 2-thiazolines presumably occurs via α-deprotonation of the substituents at the sulfur atom followed by intramolecular [1,5]-cyclization. Deprotonation of the ketimine fragment of the same molecule followed by [1,7]-electrocyclization resulted in azepine ring formation.

We have shown that (alkylsulfanyl)-substituted conjugated 2-aza-1,3,5-trienes [H_2C=CH–C(R)=C(SAlk)–N=CR_2] prepared in one preparative step from readily accessible allenes or alkynes, isothiocyanates, and alkylating agents, according to procedures developed by us,[1] can serve as direct precursors of a new series of azacycloheptadienes and azacycloheptatrienes.[2–4] The process comprises an unprecedented structural reorganization of 2-aza-1,3,5-trienes **1** into seven-membered azaheterocycles under the action of *t*-BuOK (1.2–1.5 equiv) in dry THF (0 °C, 10 min[3a] or 15 °C, 30 min[4b]), or THF/DMSO (ca. −30 °C, 30 min)[3,4] according to Scheme 1 (via in situ generation and [1,7]-azaelectrocyclization of azatrienyl anions **A**), and represents a novel, simple, and synthetically attractive approach to both dihydroazepines **2** and azepines **3**.

We have also found that the ratio of 4,5-dihydro-3*H*-azepines **2** and 3*H*-azepines **3** is strongly influenced by the structure and nature of the substituents on both the azomethine and butadiene parts of the 2-aza-1,3,5-trienes **1** as well as at the sulfur atom.

In the light of these results, we have studied the reaction of *t*-BuOK with conjugated azatrienic systems bearing unusual base-sensitive substituents at the sulfur atom, namely, (allyl-, benzyl-, and propargylsulfanyl)-substituted 2-aza-1,3,5-trienes **1a–d**. The presence of these substituents in the structure of substrates **1a–d** would not allow prediction of the result of their interaction with *t*-BuOK, which brings additional intrigue into this study.



Scheme 1.

2-Aza-1,3,5-trienes **1a–d** were prepared from α-lithiated methoxyallene, isopropyl, *sec*-butyl, or cyclohexyl isothiocyanate and allyl, benzyl, or propargyl bromide, respectively, (via the one-pot synthesis of 1-aza-1,3,4-trienes **4a–d** in yields of 87–98%, and their thermally induced sigmatropic rearrangement) (Scheme 2).

The isomerization of 1-aza-1,3,4-trienes **4a–d** into the target 2-aza-1,3,5-trienes **1a–d** was completed by heating under reduced pressure [on a rotary evaporator at 55–60 °C for 10 min followed by vacuum treatment at 50–58 °C (1 mmHg) for 5–15 min]. This

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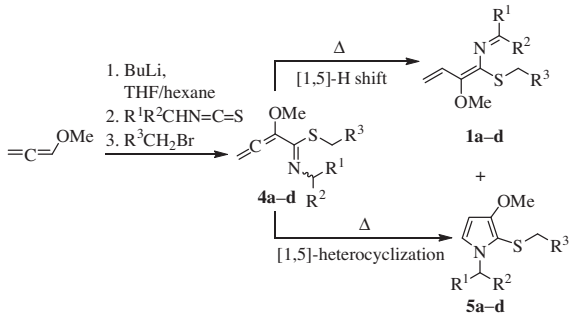
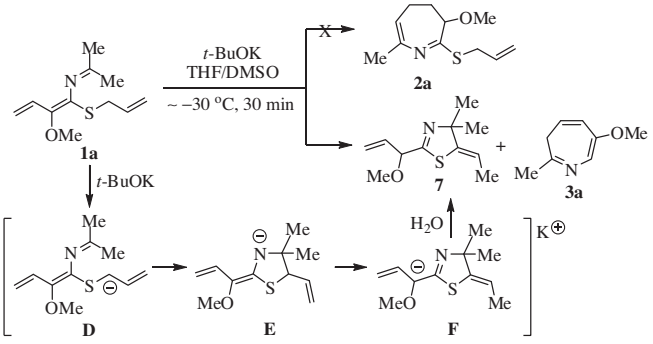


$R^1 = R^2 = Me$, $R^3 = CH{=}CH_2$ (**a**), Ph (**b**); $R^1 = Me$, $R^2 = Et$, $R^3 = C{\equiv}CH$ (**c**); $R^1,R^2 = (CH_2)_5$, $R^3 = C{\equiv}CH$ (**d**)

Scheme 2.



Scheme 4.

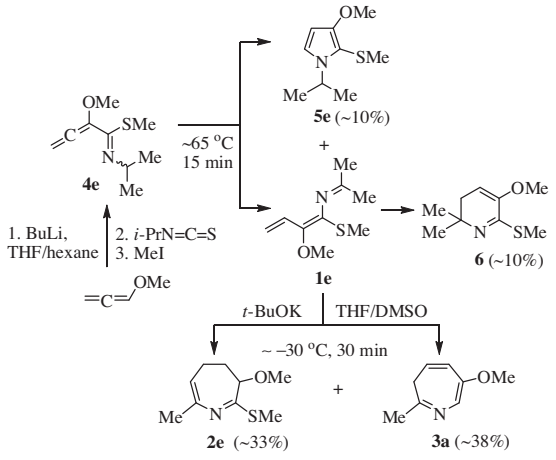
was accompanied by competitive intramolecular [1,5]-heterocyclization of **4** into pyrroles **5** (8–13% as mixtures with **1**; a trace amount in the case of **4d**) (Scheme 2), the conversion of 1-aza-1,3,4-trienes **4** being 100%. The total yield of compounds **1** and **5** is almost quantitative (94–99%).

Notably, parallel formation of pyrroles (as by-products) during sigmatropic rearrangement of 1-aza-1,3,4-trienes takes place only in the case of alkoxy-substituted derivatives.[1,3,5] Attempts to isolate 2-aza-1,3,5-trienes from the mixture with pyrroles by common techniques proved to be unsuccessful. During distillation in vacuo they cyclized into 2,3-dihydropyridines,[1,5] but upon chromatographic separation on a column with Al_2O_3 or SiO_2, complete decomposition occurred. This is why, in the reaction with *t*-BuOK, 2-aza-1,3,5-trienes **1** contaminated with pyrroles **5** were used.

It should be recalled, that treatment of the (methylsulfanyl)-substituted analog of 2-aza-1,3,5-trienes **1a–d** (azatriene **1e**) with *t*-BuOK (1.2 equiv) under unusually mild reaction conditions [THF/DMSO (5/1, v/v), −30 to −25 °C, 30 min][3a] led to simultaneous synthesis of 3-methoxy-7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepine (**2e**) and 6-methoxy-2-methyl-3*H*-azepine (**3a**) in yields of 33% and 38%, respectively (Scheme 3).

1-Isopropyl-3-methoxy-2-(methylsulfanyl)pyrrole (**5e**) and 5-methoxy-2,2-dimethyl-6-(methylsulfanyl)-2,3-dihydropyridine (**6**) were identified (^{1}H NMR) as side products of the 2-aza-1,3,5-triene **1e** synthesis.[3a]

To our surprise, (allylsulfanyl)-substituted 2-aza-1,3,5-triene **1a**, in contrast to (methylsulfanyl)-substituted analog **1e** (Scheme 3),[3a,3c] under similar conditions, reacted with potassium



Scheme 3.

tert-butoxide yielding, instead of the expected 2-(allylsulfanyl)-3-methoxy-6-methyl-4,5-dihydro-3*H*-azepine (**2a**), a product that was identified by extensive NMR studies as 5-[(*Z*)-ethylidene]-2-(1-methoxyallyl)-4,4-dimethyl-1,3-thiazole (**7**) (yield ~18%), along with 3*H*-azepine **3a** (yield ~7%) (Scheme 4).[6]

Also, the corresponding pyrrole **5a**, which was present in the starting 2-aza-1,3,5-triene **1a** (as a side product of its synthesis), was isolated (yield ~13%), the conversion of the 2-aza-1,3,5-triene **1a** being 100% (according to ^{1}H NMR).

Such a result arises from the fact that, in contrast to (methylsulfanyl)-substituted 2-aza-1,3,5-triene **1e** (Scheme 3),[3a,3c] along with the ketimine fragment, the substituent at the sulfur atom, that is, the allyl group, participates in the reaction with *t*-BuOK. Formation of 3*H*-azepine **3a** is thought to proceed via a similar mechanism to that depicted in Scheme 1 [through deprotonation of a methyl group from the ketimine moiety (N=CMe$_2$) of the 2-aza-1,3,5-trienic system **1a** (via intermediates **A–C**)]. Final elimination of the sulfide-anion ($CH_2{=}CHCH_2S^-$) from cyclic anion **C** under the reaction conditions affords 3*H*-azepine **3a**.

However, the unexpected structural transformation of 2-aza-1,3,5-triene **1a** into 4,5-dihydro-1,3-thiazole **7** likely involves the competitive deprotonation of the allylsulfanyl substituent upon treatment with *t*-BuOK, and proceeds according to Scheme 4 (via intermediates **D–F**). Activation of the SCH_2 moiety with a vinyl group makes its protons acidic enough for easy deprotonation.

Metallation of (benzylsulfanyl)-substituted 2-aza-1,3,5-triene **1b** with *t*-BuOK under very similar reaction conditions afforded a new thiazole derivative, 2-[(*Z*)-1-methoxyprop-1-enyl]-4,4-dimethyl-5-phenyl-4,5-dihydro-1,3-thiazole (**8**), along with the expected products, 2-(benzylsulfanyl)-3-methoxy-7-methyl-4,5-dihydro-3*H*-azepine (**2b**) and 3*H*-azepine **3a** (Scheme 5).

The yields of compounds **2b**, **3a**, and **8** were ~23, 5, and 20%, respectively (calculated from the ^{1}H NMR spectrum of the reaction mixture, purified from tar-like products by column chromatography).

Deprotonation at the ketimine fragment, accompanied by spontaneous [1,7]-electrocyclization of the carbanion **A** to give the aza-cycloheptadienyl anion **C** and final protolysis or elimination of the sulfide anion ($PhCH_2S^-$), leads to 4,5-dihydro-3*H*-azepine **2b** and 3*H*-azepine **3a**, respectively (Scheme 5). Competitive deprotonation of the benzylsulfanyl substituent, that is, the SCH_2 moiety activated with a phenyl group, results in the formation of 4,5-dihydro-1,3-thiazole **8**. This reaction most likely proceeds through intermediates **G–I** (Scheme 5).

The presence of pyrrole **5b** among the reaction products is caused by the above-mentioned competitive heterocyclization of the 1-aza-1,3,4-triene **4b**, which occurs during its isomerization into the 2-aza-1,3,5-triene **1b** (Scheme 2).

It should be noted that participation of the allylsulfanyl and benzylsulfanyl groups in the process of deprotonation of the