Tetrahedron Letters 55 (2014) 2495–2498

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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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ARTICLE INFO

Article history:
Received 30 September 2013
Revised 26 February 2014
Accepted 4 March 2014
Available online 12 March 2014

Keywords:
Methoxyallene
Isothiocyanates
2-Aza-1,3,5-trienes
Deprotonation
2-Thiazolines
Azepines

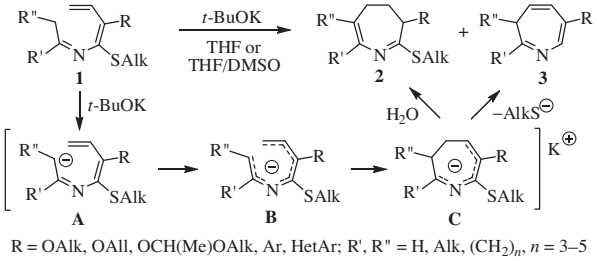
ABSTRACT

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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http://dx.doi.org/10.1016/j.tetlet.2014.03.015
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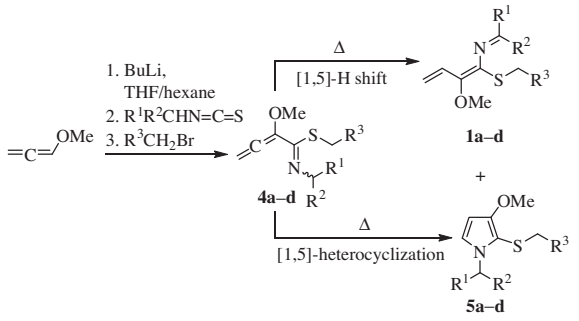
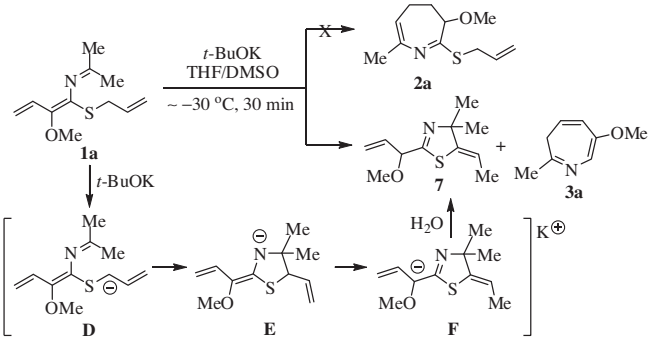


$R^1 = R^2 = Me$, $R^3 = CH{=}CH_2$ (**a**), Ph (**b**); $R^1 = Me$, $R^2 = Et$, $R^3 = C{\equiv}CH$ (**c**); $R^1,R^2 = (CH_2)_5$, $R^3 = C{\equiv}CH$ (**d**)

Scheme 2.



Scheme 4.

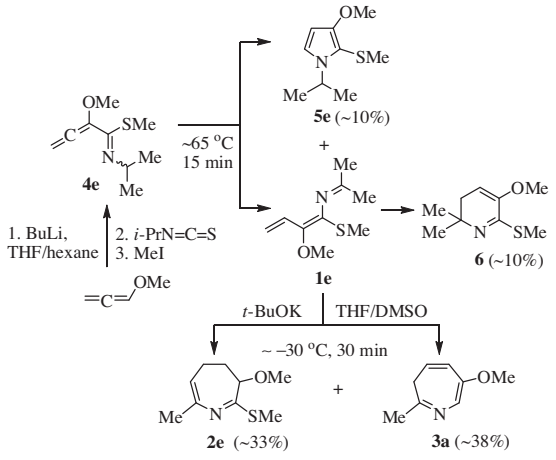
was accompanied by competitive intramolecular [1,5]-heterocyclization of **4** into pyrroles **5** (8–13% as mixtures with **1**; a trace amount in the case of **4d**) (Scheme 2), the conversion of 1-aza-1,3,4-trienes **4** being 100%. The total yield of compounds **1** and **5** is almost quantitative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

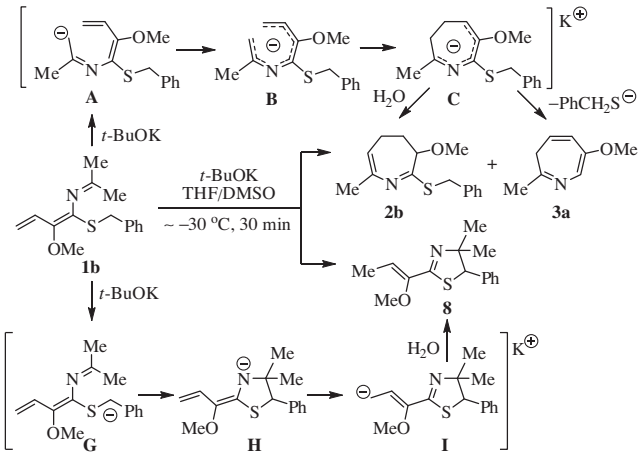
Metallation of (benzylsulfanyl)-substituted 2-aza-1,3,5-triene **1b** with *t*-BuOK under very similar reaction conditions afforded a new thiazole derivative, 2-[(*Z*)-1-methoxyprop-1-enyl]-4,4-dimethyl-5-phenyl-4,5-dihydro-1,3-thiazole (**8**), along with the expected products, 2-(benzylsulfanyl)-3-methoxy-7-methyl-4,5-dihydro-3*H*-azepine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



Scheme 5.

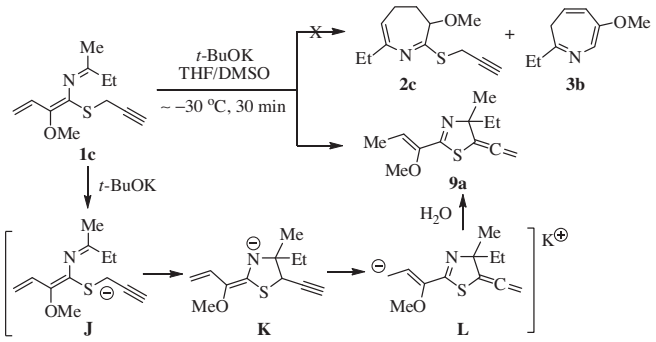
2-aza-1,3,5-trienes **1a**,**b** under the investigated conditions was not anticipated since allyl and benzyl sulfides are usually metallated by BuLi[7] or lithium amides.[7a,8] To the best of our knowledge, the use of *t*-BuOK for abstraction of allylic or benzylic protons has not yet been described. Moreover, unsymmetrically substituted allylic anions are ambident, which can react with electrophiles at two positions (α- and γ-), the selectivity of such reactions not being predictable.[9] In our case, only the product derived from the α-carbanion was obtained.

The singularity of the discussed reactions lies in the fact that in the process of structural reorganization of the 2-aza-1,3,5-triene **1b** into 4,5-dihydro-1,3-thiazole **8**, an unprecedented low-temperature (ca. −30 °C) isomerization of the 1-methoxyallyl group into a 1-methoxyprop-1-enyl group occurs. According to our[10] and the literature[11] data, allyl–propenyl isomerization in a number of allyl ethers, even in the presence of a strong base, usually takes place under harsh conditions (at temperatures above 100 °C, within several hours), and is generally very sensitive not only to the reaction parameters (solvent, base, ratio of reagents, temperature, time, etc.), but also to the allyl ether structure. Interestingly, in the case of thiazole **7**, similar isomerization of the 1-methoxyallyl group did not take place. At the same time, and typical for allyl sulfides, base-catalyzed[12] isomerization into propenyl sulfides was found to occur at low temperatures during the synthesis of thiazole **7** and appears in the transformation of the 5-vinyl group, as a part of an allyl sulfide fragment (intermediate **E**), into 5-(ethylidene) group (via intermediate **F**) (Scheme 4). While, 2-(allylsulfanyl)-1*H*-pyrrole **5a**, which was also present in the reaction mixture, did not show any tendency to isomerize into 2-(prop-1-enylsulfanyl)-1*H*-pyrrole.

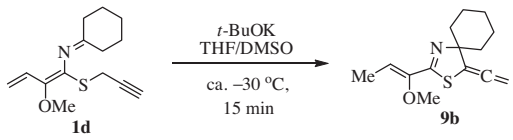
Elimination of sulfur-centered (allyl- and benzylsulfanyl)-anions from (allyl- and benzylsulfanyl)-substituted azacycloheptadienyl-anions, type **C** (Schemes 1 and 5), leading to azepine **3a**, is also unknown.

A really surprising result was obtained when (propargylsulfanyl)-substituted 2-aza-1,3,5-triene **1c**[13] was involved in the reaction with *t*-BuOK under conditions that are typical for dihydroazepine/azepine synthesis.[3,4] In this case, the reaction proceeded efficiently with high selectivity, and instead of the expected 4,5-dihydro-3*H*-azepine **2c** and 3*H*-azepine **3b**, gave 5-ethenylidene-4-ethyl-2-[(*Z*)-1-methoxyprop-1-enyl]-4-methyl-4,5-dihydro-1,3-thiazole (**9a**) as the only product in ~60% yield (crude) and ~46% (after double purification) (Scheme 6).[14]

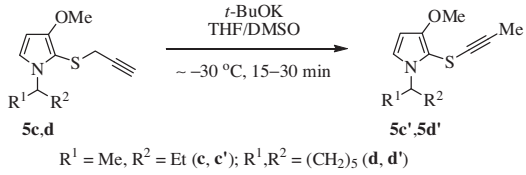
A possible mechanism for the reaction is suggested in Scheme 6. Structural reorganization of 2-aza-1,3,5-triene **1c** into thiazole **9a** probably proceeds through intermediates **J**–**L**, and includes two types of base-induced isomerization, namely allyl–propenyl and acetylene–allene, also occurring at low temperatures (Scheme 6).



Scheme 6.



Scheme 7.



Scheme 8.

Starting from (propargylsulfanyl)-substituted 2-aza-1,3,5-triene **1d**, which possesses an imino cyclohexanone moiety, spirocyclic 4,5-dihydro-1,3-thiazole **9b** was obtained under similar reaction conditions (15 min) in 23% isolated yield (Scheme 7), the conversion of 2-aza-1,3,5-triene **1d** being ~100%.

1-(*sec*-Butyl)- and 1-cyclohexyl-3-methoxy-2-(propargylsulfanyl)-1*H*-pyrroles (**5c** and **5d**, respectively), that were present in the starting compounds **1c**,**d** in small amounts (~8 and ~4%), upon reaction with *t*-BuOK isomerized into 2-(prop-1-ynylsulfanyl)-1*H*-pyrroles **5c′**[15] and **5d′** (Scheme 8).

4,5-Dihydro-1,3-thiazoles **7–9** and other heterocycles were isolated from their mixtures by column chromatography and were characterized by spectral and elemental analysis data.

In conclusion, the discovered reaction of competitive mild deprotonation of allyl-, benzyl-, and propargylsulfanyl substituents in 2-aza-1,3,5-trienes [*N*-(buta-1,3-dienyl)ketimines] under the action of the *t*-BuOK/THF/DMSO not only significantly broadens knowledge about the metallation reactions of azatrienic systems having several reaction centers, but can also be the basis for a novel approach to the simple synthesis of new classes of multifunctional 2-thiazolines, known representatives of which are used widely in medicine and pharmacology.[16] Further studies on the scope and generality of this novel methodology for thiazole ring construction, as well as optimization of the reaction conditions are in progress.

Acknowledgments

The authors are grateful for the financial support from the Russian Foundation for Basic Research (Grant No. 13-03-00691a) and the Presidium of the Russian Academy of Sciences (Project No. 8.17).

Supplementary data

Supplementary data (experimental section, characterization of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.015.

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13. *Prop-2-ynyl N-(sec-butyl)-2-methoxybuta-2,3-dienimidothioate* (***4c***). To a vigorously stirred solution of methoxyallene (4.61 g, 65.8 mmol) in THF (40 mL) was added BuLi (40.8 mmol, 25.5 mL of a ~1.6 M solution in hexane) at −100 °C under argon. The temperature was allowed to rise to −30 °C, after which the solution was cooled to −80 °C and *sec*-butyl isothiocyanate (4.45 g, 38.7 mmol) was added in one portion. The temperature of the reaction mixture was allowed to rise to ca. −30 °C, and was maintained at −33 °C to −25 °C for an additional 25 min. Next, the mixture was cooled to −80 °C and propargyl bromide (5.7 g, 47.9 mmol) was added in one portion, after which the cooling bath was removed. After stirring for 65 min at room temperature, H_2O (40 mL) was added to the mixture and cooled to −60 °C. After separation of the layers, the products were extracted from the aqueous fraction with Et_2O (3 × 40 mL). The combined organic fractions were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure (at ~1 mmHg) to give a very dark mobile liquid consisting of 1-aza-1,3,4-triene **4c** and 2-aza-1,3,5-triene **1c** as a mixture in the ratio 1:2 (by NMR). Yield: 8.11 g (94%).
2-Methoxy-N-(1-methylpropylidene)-1-(prop-2-ynylsulfanyl)buta-1,3-dien-1-amine (2-aza-1,3,5-triene ***1c***). The complete isomerization of 1-aza-1,3,4-triene **4c** into 2-aza-1,3,5-triene **1c** was effected by vacuum treatment of a sample (8.0 g, 35.9 mmol) at 56–58 °C (1 mmHg) for 15 min. The residue (7.64 g, 96%) consisted of 2-aza-1,3,5-triene **1c** (~92%) and pyrrole **5c** (~8%) (by ^{1}H NMR). ^{1}H NMR (400.13 MHz, $CDCl_3$, ppm): δ = 5.87 (1H, dd, $^3J_{trans}$ 17.2 Hz, $^3J_{cis}$ 10.9 Hz, CH═), 5.23 and 4.95 (2H, both dd, $^3J_{trans}$ 17.2 Hz, $^3J_{cis}$ 10.9 Hz, $^2J_{gem}$ 1.8 Hz, CH_2═), 3.64 (3H, s, OCH_3), 3.35 (2H, d, ^4J 2.7 Hz, SCH_2), 2.43 (2H, q, ^3J 7.4 Hz, CH_2CH_3), 2.15 (1H, t, ^4J 2.7 Hz, HC≡), 1.91 (3H, s, CH_3C═), 1.17 (3H, t, ^3J 7.4 Hz, CH_2CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, ppm): δ = 179.08 (C═N), 138.53 (═C–O), 126.58 (═C–S), 126.33 (CH═), 110.90 (CH_2═), 80.93 (C≡), 70.57 (HC≡), 58.90 (OCH_3), 34.59 (SCH_2), 20.69 (CH_3C═), 17.71 (CH_2), 10.46 (CH_2CH_3). IR (cm^{-1}): 3293 (≡CH), 2969, 2933, 2876, 2828, 2272, 1645, 1607, 1565, 1545, 1460, 1438, 1398, 1367, 1332, 1258, 1237, 1187, 1155, 1067, 1047, 977, 953, 893, 788, 707, 644.
14. *Treatment of 2-Aza-1,3,5-triene* ***1c*** *with t-BuOK*. To a stirred solution of the product mixture (7.58 g, 34 mmol) containing ~92% of 2-aza-1,3,5-triene **1c** and ~8% of pyrrole **5c** in THF (51 mL), DMSO (11 mL) and *t*-BuOK (4.25 g, 37.9 mmol) were added sequentially at −60 °C. The mixture was stirred for 30 min while the temperature was kept between −35 °C and −30 °C, and was then cooled to −70 °C, and H_2O (40 mL) was added. After separation of the layers, the products were extracted from the aqueous fraction with Et_2O (4 × 40 mL). The combined organic fractions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$). Flash column chromatography of the solution on alumina (2 cm layer) followed by concentration under reduced pressure gave 6.54 g (86%) of a dark-brown mobile liquid consisting of 4,5-dihydro-1,3-thiazole **9a** (~74%), pyrrole **5c′** (~10%), and an unidentified product (~16%) (by ^{1}H and ^{13}C NMR). 4,5-Dihydro-1,3-thiazole **9a** was separated by column chromatography (neutral alumina, hexane) in a yield of 3.2 g (~46%). Pyrrole **5c′** was identified by NMR in the mixture with thiazole **9a** in one of the small fractions.
*5-Ethenylidene-4-ethyl-2-[(Z)-1-methoxyprop-1-enyl]-4-methyl-4,5-dihydro-1,3-thiazole (****9a****)*. Brownish viscous liquid, n_D^{23} 1.5481. ^{1}H NMR (400.13 MHz, $CDCl_3$, ppm): δ = 5.74 (1H, q, ^3J 6.9 Hz, CH_3CH═), 5.12 and 5.10 (1H, d, ^2J 10.2 Hz, CH_2═C═), 3.68 (3H, s, OCH_3), 1.91 and 1.64 (2H, dq, ^3J 7.4 Hz, ^2J 13.6 Hz, CH_2CH_3), 1.77 (3H, d, ^3J 6.9 Hz, CH_3CH═), 1.42 (3H, s, CH_3-4), 0.86 (3H, t, ^3J 7.4 Hz, CH_2CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, ppm): δ = 198.04 (═C═), 158.36 (C═N), 149.54 (═C–O), 119.41 (CH_3CH═), 109.43 (═C–S), 85.01 [$C(C_2H_5)CH_3$], 83.52 (CH_2═C═), 59.78 (OCH_3), 34.83 (CH_2CH_3), 27.76 (CH_3CH═), 11.03 (CH_3-4), 8.71 (CH_2CH_3). IR (cm^{-1}): 3043, 2971, 2932, 2878, 2854, 2841, 1954, 1652, 1604, 1457, 1446, 1435, 1377, 1367, 1329, 1308, 1290, 1241, 1222, 1201, 1192, 1154, 1137, 1113, 1097, 1072, 1041, 1000, 977, 929, 896, 891, 864, 824, 812, 786, 711, 687, 681. Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.40; H, 7.75; N, 6.47; S, 14.10.
15. *1-(sec-Butyl)-3-methoxy-2-(prop-1-ynylsulfanyl)-1H-pyrrole (****5c′****)*. ^{1}H NMR (400.13 MHz, $CDCl_3$, ppm): δ = 6.65 (1H, d, ^3J 3.3 Hz, H-5), 5.89 (1H, d, ^3J 3.3 Hz, H-4), 4.52 (1H, tq, ^3J 6.8 Hz, J 7.1 Hz, $CHCH_3$), 3.82 (3H, s, OCH_3), 1.84 and 1.77 (2H, both m, CH_2CH_3), 1.82 (3H, s, CH_3C≡), 1.38 (3H, d, ^3J 6.8 Hz, $CHCH_3$), 0.82 (3H, t, ^3J 7.4 Hz, CH_2CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, ppm): δ = 151.23 (C-3), 118.00 (C-5), 102.48 (C-2), 95.06 (C-4), 67.90 (CH_3C≡), 58.34 (OCH_3), 55.53 (SC≡), 53.27 (NCH), 30.60 (CH_2CH_3), 21.70 ($CHCH_3$), 10.77 (CH_2CH_3), 4.76 (CH_3C≡).
16. Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140–4182.