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Elemental sulfur as a trigger and reagent in cyclization of γ-amino acetylenic ketones to 1,2-dihydro-3*H*-pyrrole-3-thiones

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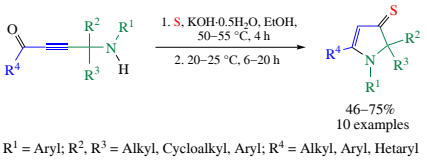
An original and effective synthesis of 1,2-dihydro-3*H*-pyrrole-3-thiones from available γ-amino acetylenic ketones and elemental sulfur as a trigger and reagent has been developed. The reaction is carried out in the KOH/ethanol system, the yield of the target heterocycles being 46–75%.



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Pyrrolethiones and their derivatives are in-demand class of heterocyclic compounds, especially due to their application in pharmaceutical synthesis.[1–9] For example, ammosamide A (a natural alkaloid) containing a pyrrolethione moiety possesses *in vitro* cytotoxicity against colon carcinoma.[1] Phytoalexins of natural origin with fungicidal properties have been synthesized based on pyrrolethione derivatives.[2] 3-Substituted benzylidene-1,3-dihydroindolethiones containing pyrrolethione structural elements act as inhibitors of human protein kinases.[3] In addition, pyrrolethione analogs exhibit pronounced antibacterial,[4] antituberculosis,[5] anti-HIV,[6] antiviral[7] and antitumor[8] activities. Pyrrolethiones are employed as fluorescent sensors for the determination of mercury ions in living systems.[9] It is also known that pyrroles with thione functions are used as effective building blocks in organoelement chemistry.[10–12]

However, this type of heterocycles is represented mainly by pyrrole systems with a 2-positioned thione group.[1–12] The data on pyrrole-3-thiones are limited, as far as we know, to one work,[13] which reported their preparation by the thionation of pyrrol-3-ones with P_2S_5. Therefore, the search for alternative methods for the synthesis of such compounds is urgent. It should be noted that we have recently developed an approach to 1,2-dihydro-3*H*-pyrrole-3-thiones based on propargylamines, acyl chlorides and sodium sulfide.[14]

Meanwhile, the development of alternative method for the synthesis of 1,2-dihydro-3*H*-pyrrole-3-thiones using amino acetylenic ketones and cheaper and more available elemental sulfur as thione functionality generator would be useful contribution to the chemistry of these heterocycles. The starting amino acetylenic ketones are now available through the recently developed chemoselective cross-coupling of propargylamines with aromatic and heteroaromatic acyl chlorides in the presence of the Et_3N/CuI/$PdCl_2$/Ph_3P system.[15,16] The key step in their assembly, the reaction of acetylenes with C=N-bonded compounds, has been recently used for the preparation of pyrrolines[17] and pyrazoles.[18]

An important issue here is also the extension of the application of elemental sulfur (with its vast resources) as a convenient and safe reagent in organic synthesis.[19,20] There are data published on the direct reaction of acetylenes with elemental sulfur in the presence of bases to form the C_{sp2}–S bond.[19,21–23] In particular, acetylene or diacetylene react with elemental sulfur in the KOH/DMSO system to provide divinyl sulfide or thiophene, respectively.[21–24] It was also reported on the synthesis of functional thiophenes by the reactions of internal acetylenic ketones or acetylenedicarboxylic diesters with elemental sulfur in the presence of potassium hydroxide or pyridine.[25,26] The fundamental possibility of the formation of the C=S bond is presented by a study of the three-component reaction of 1-substituted imidazoles, 1-cyano-2-phenylacetylene and elemental sulfur, which opens access to the stereoselective synthesis of (*Z*)-3-(2-cyano-1-phenylethenyl)imidazole-2-thiones.[27]

In continuation of research along this line, we herein report that γ-amino acetylenic ketones **1a–k** react with elemental sulfur in the KOH/ethanol system to afford 1,2-dihydro-3*H*-pyrrole-3-thiones **2a–k** in 46–75% yields (Scheme 1). The developed one-pot process is implemented as follows: heating (50–55 °C, 4 h) of elemental sulfur in the KOH/EtOH system, followed by the addition of acetylenic ketone **1** and maintaining the reaction mixture at room temperature for 6–20 h.† The reaction was monitored by TLC following the disappearance of the spot of the initial electron-deficient acetylene **1**, as well as by IR spectroscopy by the presence of a triple bond absorption band in the region of ~2208 cm^{-1}. It should be noted that the direct mixing of elemental sulfur,

† *Preparation of 1,2-dihydro-3*H*-pyrrole-3-thiones* **2** *from γ-amino acetylenic ketones* **1**, *elemental sulfur and KOH·0.5H_2O*. A suspension of elemental sulfur (35.2 mg, 1.1 mmol) and KOH·0.5H_2O (143 mg, 2.2 mmol) in EtOH (3 ml) was stirred under argon atmosphere at 50–55 °C for 4 h. Then γ-amino acetylenic ketone **1a–k** (1.0 mmol) was added to the obtained suspension, and the reaction mixture was stirred at 20–25 °C for 6–20 h (see Scheme 1). After completion of the reaction (TLC monitoring, eluent: toluene/Et_2O, 10 : 1), the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 (eluent: toluene/Et_2O, 10 : 1), the proper fractions were concentrated *in vacuo* to afford the corresponding 1,2-dihydro-3*H*-pyrrole-3-thione **2a–k**.

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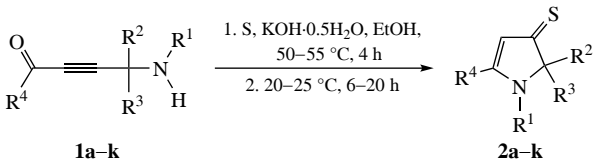


1a–k **2a–k**

a $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = Cy$ (59%)
b $R^1 = R^3 = R^4 = Ph$, $R^2 = Me$ (75%)
c $R^1 = R^3 = Ph$, $R^2 = Me$, R^4 = 2-furyl (62%)
d $R^1 = R^3 = Ph$, $R^2 = Me$, R^4 = 2-thienyl (71%)
e $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = 4\text{-}ClC_6H_4$ (61%)
f $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = 4\text{-}EtC_6H_4$ (73%)
g $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = 4\text{-}MeOC_6H_4$ (68%)
h $R^1 = R^2 = R^3 = R^4 = Ph$ (< 5%)
i R^1 = 1-naphthyl, $R^2 = R^3 = Me$, $R^4 = Ph$ (61%)
j $R^1 = Ph$, $R^2 + R^3 = (CH_2)_5$, R^4 = 2-thienyl (66%)
k $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = Pr^i$ (46%)

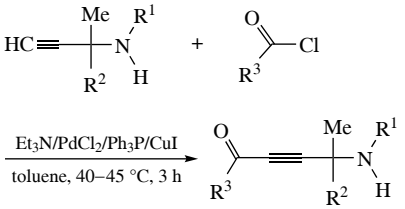
Scheme 1 *Reagents and conditions*: S (elemental, 35.2 mg, 1.1 mmol), $KOH{\cdot}0.5H_2O$ (143 mg, 2.2 mmol), EtOH (3 ml), 50–55 °C, 4 h, then amino acetylenic ketone **1a–k** (1.0 mmol), 20–25 °C. Reaction time: 6 h for **1b–e**,**j**, 8 h for **1f**,**g**, 10 h for **1h**,**i**, 12 h for **1a** and 20 h for **1k**.

potassium hydroxide and amino acetylenic ketone **1a** at 50–55 °C gave a worse result. In this case, the target 1,2-dihydro-3*H*-pyrrole-3-thione **2a** was isolated in low yield (~25%), the main direction of the process being the competitive formation of the corresponding 1,2-dihydro-3*H*-pyrrol-3-one.[15]

The efficiency of the reaction was also influenced by the nature of the substituents in the starting acetylenic ketones **1**. A moderate 46% yield of pyrrolethione **2k** (see Scheme 1) and a longer reaction time are apparently due to the electron-donating isopropyl substituent that reduces the electrophilicity of the triple bond of the starting amino acetylenic ketone **1k**. Along with the electronic factors, the yields of target heterocycles **2** are affected by steric surrounding of the reaction center. Thus, the bulky aliphatic cyclohexyl group in the acyl fragment of substrate **1a** decreases accessibility of the ketone group and, as a consequence, increases the reaction time to 12 h and reduces the yield of the target pyrrolethione **2a** to 59%. The introduction of two phenyl substituents at the quaternary carbon in the propargyl part of the acetylenic ketone **1h** makes the triple bond more sterically shielded, thereby reducing its reactivity. As a result, 1,2-dihydro-3*H*-pyrrole-3-thione **2h** was identified in the reaction mixture in small quantities (less than 5%, ^{1}H NMR data).

It should be noted that, along with the previously obtained amino acetylenic ketones **1a–f**,**h**,**j**,**k**,[15,16] two new representatives of γ-amino acetylenic ketones **1g**,**i** were synthesized in this work based on the similar methodology (Scheme 2).‡

The structures of all obtained compounds **2** were unambiguously proven by IR, NMR (^{1}H and ^{13}C) spectroscopy, including homonuclear and heteronuclear 2D COSY, HSQC and HMBC NMR. Thus, in the ^{1}H NMR spectra the characteristic signal of pyrrole-3-thiones belongs to the H^4 proton of the heterocyclic fragment in the region of 6.61–6.93 ppm and the signal for the methyl group in dihydropyrrolethiones **2a–g** is located in the region of 1.68–



1g,**i**

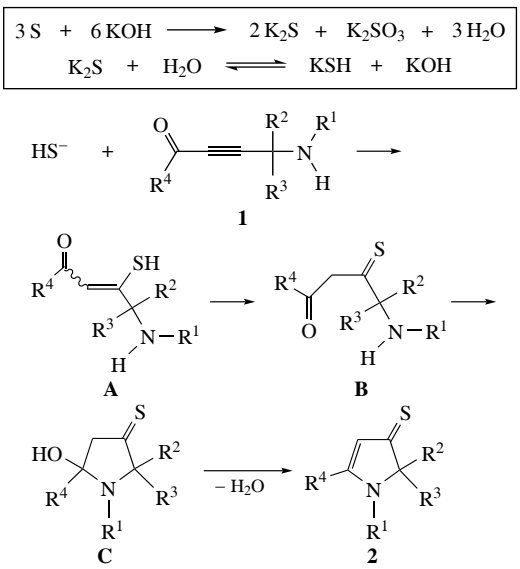
1g $R^1 = R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4$ (88%)
1i R^1 = 1-naphthyl, $R^2 = Me$, $R^3 = Ph$ (72%)

Scheme 2

1.75 ppm. In this case, the signals for other protons are not characteristic. In the ^{13}C NMR spectra, the dihydropyrrolethione ring appears as separate singlet signals. Thus, the C^4 signal is located in the region of 112.9–122.4 ppm, the signals for the quaternary C^2 atom and C^5 are observed in the region of 82.5–87.7 and 159.9–172.6 ppm, respectively. Also, a characteristic signal for the pyrrolethione ring is the carbon signal of the C=S fragment in the region of 217.1–227.7 ppm. The individual purity of the synthesized products was established using elemental analysis.

The assembly of 1,2,5-trisubstituted-1,2-dihydro-3*H*-pyrrole-3-thiones **2** from amino acetylenic ketones **1** involves the initial generation of potassium hydrosulfide by the hydrolysis of potassium sulfide (formed upon the cleavage of elemental sulfur with potassium hydroxide) with water (Scheme 3). Next, the hydrosulfide anion nucleophilically adds to the triple bond of electron-deficient acetylene to form the corresponding vinylic thiol **A**. The prototropic isomerization of the latter gives keto thione **B**, thereby providing the possibility of intramolecular nucleophilic addition of the amino group to the carbonyl fragment. The resulting hydroxypyrrolidine-3-thione **C** undergoes dehydration to yield the final 1,2-dihydro-3*H*-pyrrole-3-thione **2**. We did not detect the formation of polyfunctional divinyl sulfides, possible products of further addition of a thiol (intermediate **A**) to the triple bond of the starting acetylene **1**, in the reaction mixture.

In summary, we have developed an alternative method for the synthesis of 1,2-dihydro-3*H*-pyrrole-3-thiones using the direct reaction of elemental sulfur as a trigger and reagent with available amino acetylenic ketones in the KOH/ethanol system. The results contribute to a wider application of elemental sulfur as a convenient reagent in organic synthesis. The synthesized 1,2-dihydro-3*H*-pyrrole-3-thiones are promising ligands for



Scheme 3

‡ *Synthesis of γ-amino acetylenic ketones* **1g**,**i**. To a solution of the corresponding propargylic amine (2.0 mmol) and acyl chloride (2.0 mmol) in toluene (5 ml), CuI (0.016 g, 0.08 mmol), $PdCl_2$ (0.006 g, 0.04 mmol), Ph_3P (0.01 g, 0.04 mmol), and Et_3N (1 ml) were added. The mixture was stirred under argon at 40–45 °C for 3 h (see Scheme 2). After completion of the reaction (TLC monitoring, eluent: hexane/Et_2O, 2 : 1), the solvent was removed under reduced pressure, the residue was purified by flash-chromatography on basic Al_2O_3 (eluent: toluene), the proper fractions were concentrated *in vacuo* to afford the corresponding amino acetylenic ketones **1g**,**i**.

design of coordination compounds, building blocks in organic synthesis, as well as precursors of biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7582.

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