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A NEW CONVENIENT METHOD TO OBTAIN PYRROLES FROM TERTIARY N-ALLYLTHIOAMIDES.

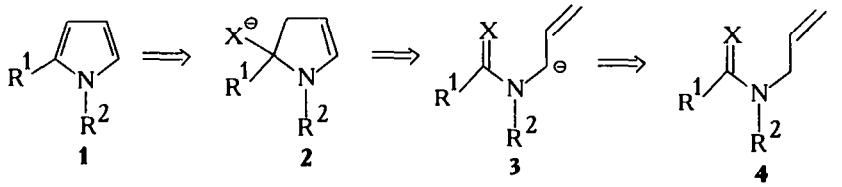
IGOR V. MAGEDOV* , ALEXANDER V. KORNIENKO, TATYANA O. ZOTOVA and VICTOR N. DROZD*

Department of Organic Chemistry, Timiryazev Agricultural Academy, Timiryazevskii proezd 2, Moscow 127550, Russia.
Fax: (095) 976-18-20

Abstract: 1,2-Disubstituted pyrroles **1** were synthesized from available thioamides **4**. Thioamides were initially treated with either alkylating agents or Lewis acids to give salts **5** or complexes **12** which were subsequently reacted with base to yield pyrroles **1**.

Heterocyclic system of pyrrole is widely spread in nature. There are a lot of methods for the synthesis of pyrroles from simple aliphatic precursors[1]. In the present paper we report of a new convenient method for the synthesis of 1, 2-disubstituted pyrroles from tertiary N-allylthioamides. The retrosynthetic analysis of a pyrrole molecule **1** leads to accessible N-allylamides (thioamides) **4** (Scheme 1). The key intermediate is the α'-metallated tertiary N-allylamide (thioamide) **3**.

Scheme 1



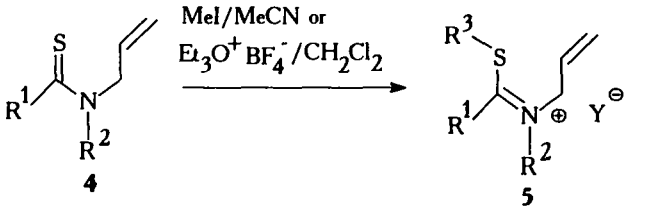
X= O; S

In general allyl organolithium reagents bearing a terminal nitrogen have proven to be of synthetic importance[2]. A number of tertiary allyl amides and their analogues have been found to undergo α'-lithiation to give dipole stabilized carbanions[3]. Beak[4] and Seebach[5] have shown that sterically unhindered α'-lithiated N-allylamides do not undergo formally allowed, according to Baldwin rules for ring closure, 5-exo-trig cyclization but react in intermolecular fashion to give self-condensation products. By means of NMR spectroscopy Beak[6] has shown that a major part of a negative charge in the anion **3** is localized in position α'. In addition to that fact the molecular model investigation shows that the intramolecular cyclization requires the rotation of the terminal γ '-carbon by the angle of 90° which liberates the latter from the allylic delocalization. The combination of both factors presumably increases the activation energy for the cyclization.

We have solved the above problem by converting the exo-thiocarbonyl group into the endo-immonium one that in the presence of another endo-double bond of the allylic fragment leads to the change in the

mechanism of the reaction : from the nucleophilic addition to 1,5-dipolar cyclisation. The choice of thioamides as starting materials was due to easiness of their interaction with electrophilic reagents. The conversion of thioamides **4** into thioamidium salts was accomplished in two ways: (i) alkylation; (ii) formation of complexes with Lewis acids. Thioamidium salts **5** were synthesized by alkylation of thioamides **4** with MeI in acetonitrile or $Et_3O^+ BF_4^-$ in CH_2Cl_2 (Scheme **2**). Noncrystallizing (oily) S-alkyl thioamidium salts **5** were used without purification.

Scheme **2**



The reaction of DABCO, TMEDA, NEt_3 with the salts **5a** gave amides **4a** as a sole product. However the reaction of the salts **5a-d** with 2,2 eq. of LiHMDS afforded corresponding pyrroles **1a-d** in 17-43 % yields (see Scheme **3** and Table **1**) as well as dealkylation products i.e.thioamides **4a-d** in 10-30 % yields. The low yield of 1-benzyl-2-phenyl pyrrole **1d** is probably due to the close value of acidity for allylic and benzylic fragments. In the case of S-ethyl salt **5e** the main product was the thioamide. This fact can be understood having in mind the possible deethylation of the salt **5e** by the E2 mechanism .

The following mechanism was originally proposed for this reaction (Scheme **3**): (i) Salt **5** being deprotonated gives the zwitter ion **10**; (ii) The latter undergoes 1,5-dipolar cyclisation to give **11**; (iii) **11** is converted into pyrrole **1**.

Scheme **3.**

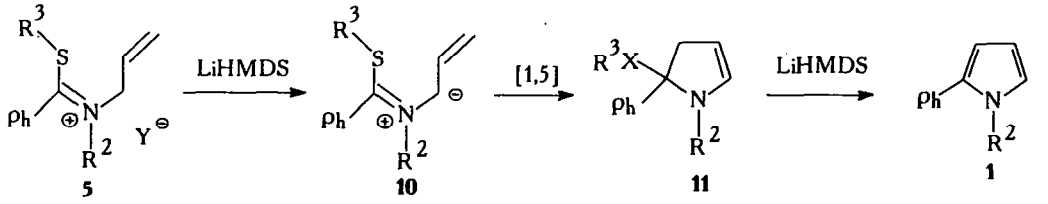
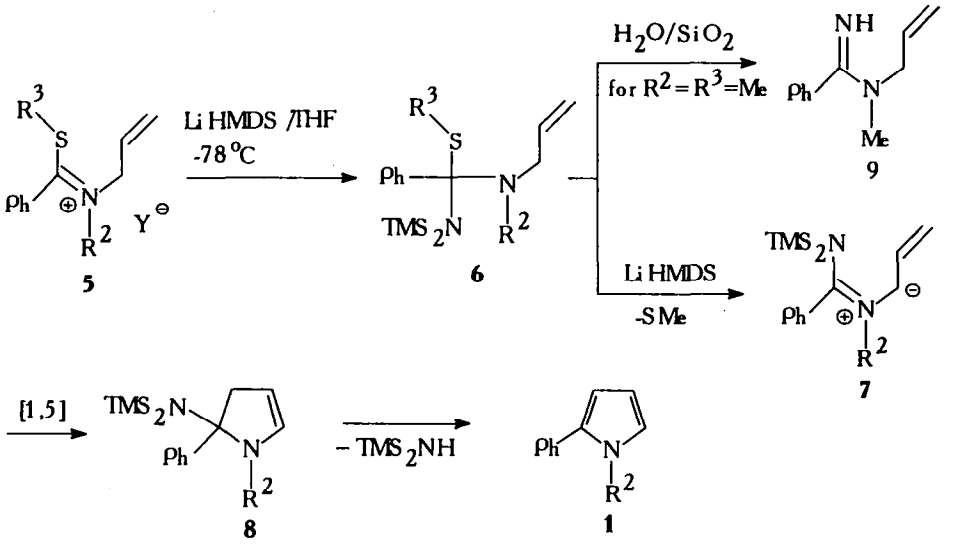


Table 1: Pyrroles from thioamides:

Pyrrole	Alkylation Agent or Lewis Acid (LA)	Yield (%)/ Time (h)	Pyrrole	Alkylation Agent or Lewis Acid (LA)	Yield (%)/ Time (h)
1a	MeI	32/1	**1b**	MeI	33/1
1a	$Et_3O^+ BF_4^-$	5/1	**1b**	BCl_3	17/24
1a	BCl_3	47/24	**1c**	MeI	43/48
1a	BF_3OEt_2	43/24	**1c**	BCl_3	trace/48
1a	$AlCl_3$	38/24	**1d**	MeI	19/48
1a	$SnCl_4$	trace/24	**1d**	BCl_3	trace/48

However, the chromatographic control of the reaction allowed us to find that the salts **5a-d** are converted into an intermediate which gives the final pyrrole. Using 1,1 eq. of LiHMDS the intermediate was isolated in 30% yield and identified as N-allyl-N-methyl benzamidine **9**. These data must be in accord with the following mechanism (Scheme **4**): (i) LiHMDS adds to the salt **5** with the formation of the intermediate **6**; (ii) Elimination of MeS- and deprotonation by the second equivalent of LiHMDS gives the zwitter ion **7**; (iii) The latter undergoes cyclization and aromatization to give pyrrole **1**.

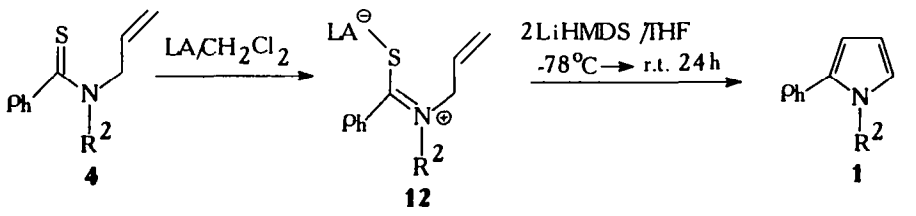
Scheme **4**



a R^2 = Me; **b** R^2 = Et; **c** R^2 = Ph; **d** R^2 = $PhCH_2$.

It was published earlier that BF_3 complexes with pyridine and tertiary amines react smoothly with LiTMP to yield α-lithiated species[7]. It is also known[8], that thioamides form rather stable complexes with Lewis acids. It occured to us that coordination complexes of thioamides with Lewis acids treated with bases would yield pyrroles **1 a-d**. Using LiHMDS as a base we really obtained pyrroles (see Scheme **5** and Table **1**). As can be seen from the Table 1, the best yield of pyrroles was achieved using BCl_3 as a Lewis acid. However the reaction proceeds rather slowly and sterically hindered N-Ph and N-Bn thioamides **4 c,d** do not give good yields even after 5 days of the reaction.

Scheme **5.**



Typisal experiments. Method **A:** A solution of **5 a-d** (4mmol) in CH_2Cl_2 was added with stirring under argon at -78 °C to a solution of LiHMDS (10mmol) in THF. The mixture was stirred for 1h at -78 °C and then allowed to reach room temperature. In cases **5 c,d** the mixture was allowed to stand at room temperature for additional 48h. H_2O was added, organic layer was separated and the H_2O layer was extracted with CH_2Cl_2 . Combined organic layers were dried (Na_2SO_4), evaporated and chromatographed in L 100/160 silica gel (CCl_4/ Hexane 1:1). Method **B**: A mixture of thioamide **4 a-c** (4mmol) and Lewis acid (4mmol) in CH_2Cl_2 was added with stirring under argon at -78 °C to a solution of LiHMDS (10mmol) in THF. The mixture was stirred for 30 min at -78 °C, allowed to reach room temperature and stand for additional 24-48h. The product was isolated like in method A.

The starting thioamides were obtained from available N-substituted allylamines by benzoylation and thionation with Lawesson reagent .

We also tried to synthesize pyrroles from carboxamides, however, we got worse results. It can be explained by higher reactivity of O-Et amidium salts in dealkylation and lower stability of their coordination complexes with Lewis acids.

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