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Synthesis of 6-amino-2,3-dihydropyridine-4-thiones *via* novel efficient thioenolate-carbodiimide rearrangement

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Abstract

A new and efficient method for the synthesis of 6-amino-2,3-dihydro-4-pyridinethiones from *N*-(3-butenyl)thioureas, without the use of conventional thiophosphorus reagents has been reported. Thioureas are initially transformed into iodocyclothiocarbamates which subsequently give cyclic thioenol esters after base-mediated HI elimination. These esters readily undergo a base-mediated (*t*BuOK) thioenolate-carbodiimide rearrangement, accompanied by C-S bond cleavage and C-C bond formation, to finally give a series of novel 6-amino-2,3-dihydropyridine-4-thiones.

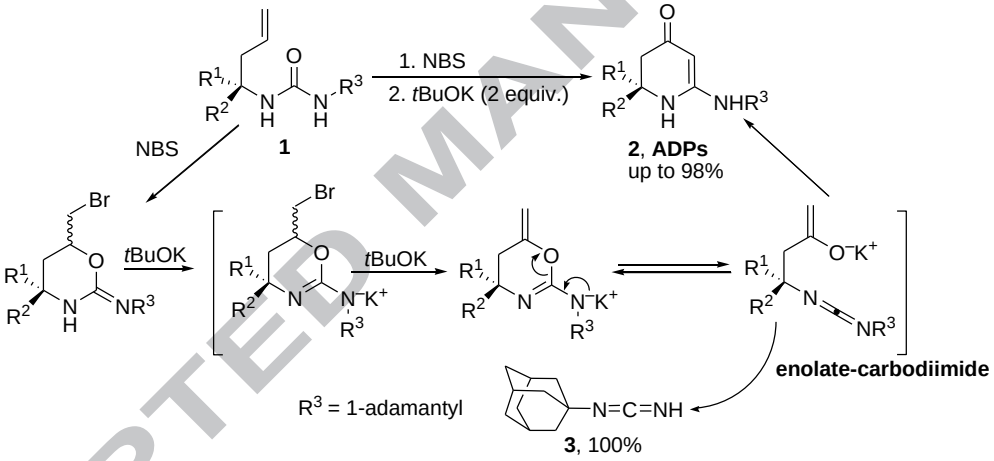
Introduction

Thiocarbonyl compounds are useful reagents and intermediates that are widely applied in the syntheses of various substances including complex biologically active molecules or natural products.[1] Due to the relatively weak C=S bond (BDE 105.3 kcal mol^{-1} in CS_2 versus 127.2 kcal mol^{-1} in CO_2),[2] thiocarbonyl compounds demonstrate high reactivity in nucleophilic addition, deprotonation, oxidation, sigmatropic rearrangement, and a variety of cycloaddition reactions with 1,3-dienes and 1,3-dipoles.[1] A general approach to the introduction of a C=S group is the direct thionation of carbonyl derivatives by treatment with hydrogen sulfide, bis(trimethylsilyl)sulfide or thiophosphorus compounds (P_4S_{10}, P_2S_5•2Py, Lawesson's and Davy's reagents).[3] Despite the well described procedures for thionation with these reagents,

† Single crystal X-Ray analysis

common drawbacks are associated with the high toxicity and unpleasant smell of sulfur-containing by-products.[4] The P_2S_5•2Py reagent seems to be an exception due to its more acceptable properties.[5] Therefore, new mild and efficient methods for the synthesis of thiocarbonyl compounds are required.

Recently, we reported an efficient transformation of *N*-(3-butenyl)ureas **1** into 6-amino-2,3-dihydro-4-pyridinones (ADPs) **2** (Scheme 1).[6] The latter can serve as useful building blocks for the synthesis of pharmaceutically relevant compounds containing the piperidine-type pharmacophore. Generally the transformations of **1** into **2** proceed smoothly, however, in cases where R^3 is a bulky group (*t*Bu, 1-adamantyl) decomposition of the intermediate enolate-carbodiimide becomes a major process, leading to the formation of carbodiimide **3** (R^3 = 1-Ad).



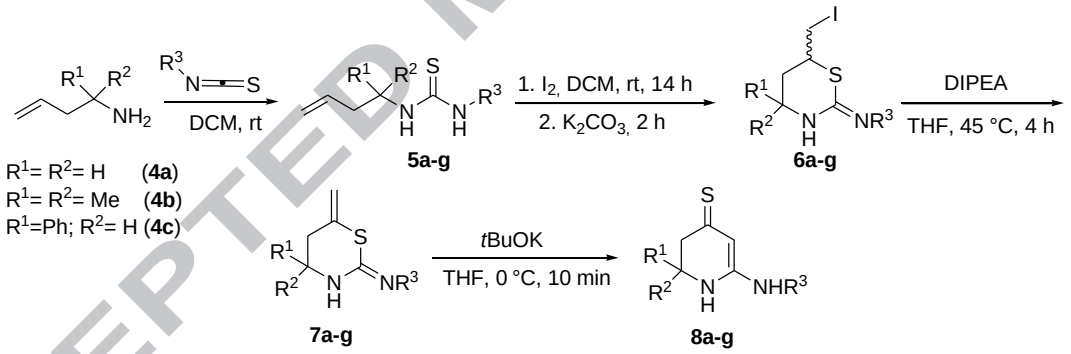
Scheme 1. Synthesis of 6-amino-2,3-dihydro-4-pyridinones (ADPs) from *N*-(3-butenyl)ureas *via* enolate-carbodiimide rearrangement.

In order to overcome this shortcoming and to broaden the scope of the synthetic methodology, we have extended this process to the synthesis of novel 6-amino-2,3-dihydro-4-pyridinethiones. The synthesis of various linear and cyclic enaminothioketones was reviewed by Usov and Voronkov.[7] Meanwhile, piperidine-4-thione derivatives are sporadically mentioned in the literature. The synthesis and application of 4-thio-derivatives of piperidine have attracted special attention from Chou's group,[8] where a number of piperidine alkaloids (indolizidines 167E and 209D, epimyrtine, lasubine II) were successfully synthesized from 4-(phenylthio)-5,6-dihydro-2(1*H*)-pyridinone. Recently a number of rare alkylthio-substituted 2-quinolinones which are expected to be useful building blocks in the synthesis of compound libraries for the screening of biological activity were synthesized by palladium-catalyzed reactions.[9] Additionally, there is

an interesting study devoted to the bioactivation of an antithrombotic prodrug, clopidogrel, where the key intermediate is believed to be a 4-mercapto-piperidine derivative.[10] Taking in account the important biological activity of 4-thiono-piperidine derivatives and their synthetic potential, herein, we present our research towards the synthesis of 6-amino-2,3-dihydro-4-pyridinethiones.

Results and Discussion

In the presented method *N*-(3-butenyl)thioureas **5a-g** were used as starting material for the preparation of 6-amino-2,3-dihydropyridine-4-thiones **8a-g**. Thioureas **5a-g** were obtained in high yields (71-99%) from the reaction of homoallylamines **4a-c**[6] with the corresponding thioisocyanates in DCM. Usually, (bromomethyl)urethanes (Scheme 1) are used as rearrangement precursors because it is more convenient to work with NBS than with free halogens, and the more important bromides provide excellent yields of the final keto-derivatives.[11,6]



Scheme 2. Synthesis of 6-amino-2,3-dihydropyridine-4-thiones **8** from homoallylamines **4**

Table 1. Transformation of *N*-(3-butenyl)thioureas **5a-g** into 6-amino-2,3-dihydropyridine-4-thiones **8a-g**.

R^1	R^2	R^3	**5** yield (%)	**6** yield (%)	**7** yield (%)	**8** yield (%)
H	H	Ph	**5a**, 87	**6a**, 80	**7a**, 92	**8a**, 95
Me	Me	Ph	**5b**, 95	**6b**, 90	**7b**, 90	**8b**, 95
Ph	H	Ph	**5c**, 96	**6c**, 80[a]	**7c**, 94	**8c**, 93
H	H	Ad	**5d**, 71	**6d**, 81	**7d**, 97	**8d**, 20
H	H	*t*Bu	**5e**, 99	**6e**, 93	**7e**, 95	**8e**, 25

Ph	H	Bn	**5f**, 97	**6f**, 91[b]	**7f**, 98	**8f**, 89
Ph	H	Me	**5g**, 97	**6g**, 91[c]	**7g**, 99	**8g**, 82

[a] *d.r.* 5.3:1; [b] *d.r.* 4.8:1; [c] *d.r.* 4:1

However, when NBS was added to thiourea **5b**, a vigorous exothermic reaction was observed with no cyclization product formation, presumably due to halogenation of the sulfur atom. In contrast to the bromides, (iodomethyl)thiourethanes were formed cleanly when ureas **5a-g** were treated with molecular iodine in DCM (14 h) followed by the addition of powdered K_2CO_3 for 2 h to complete the reaction. Iodides **6c**, **6f,g** were formed as mixtures of *cis/trans*-isomers with ratios of 4:1 to 5.3:1 (Table 1) which after consecutive crystallizations was improved to 10-25:1 with predominance for the *cis*-isomers. Attempts to carry out the direct transformation of iodides **6a-g** into thiones **8** with *t*BuOK were ineffective due to the formation of an inseparable mixture of by-products. These results are in sharp contrast to the reported patent,[12] where the addition of excess *t*BuOK to iodo-derivatives resulted in HI elimination and the formation of thioenol esters. In the work of Creeke and Mellor,[13] dehydroiodination of (iodomethyl)thiourethanes was performed by treatment with bases such as Et_3N, pyrrolidine and DBU. We found that heating iodides **6a-c** at 45 °C in THF with 2 equiv. of DBU gave rise to the elimination products **7a-c** in low yields (21-44%). Prolonged heating of the reaction mixture for these substrates did not improve the reaction outcome. Elucidation of the reaction mixture of **6c** by NMR spectroscopy revealed that large quantities of product **7c** were lost due to alkylation side-reactions of DBU by **6c**. In fact, it was reported that DBU is not an inert base and can be a good nucleophile in reactions with alkylhalides.[14] Optimization of the reaction parameters for **6a** showed that DBU and Et_3N were also prone to alkylation side-reactions at ambient temperature (Table 2, entries 1-3) and were unsuitable as bases for the elimination reactions.

Table 2. Optimization of the HI-elimination reaction for **6a→7a**.

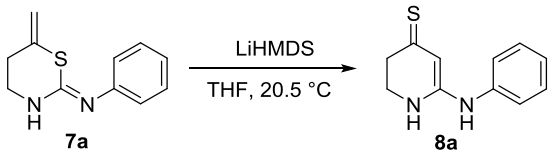
Entry[a]	Base	Solvent	Temp (°C)	Time (h)	Yield[b] **7a** (%), (**6a**,%)
1	DBU	THF	r.t.	overnight	32 (27)
2	DBU	THF	45	4	44 (0)
3	Et_3N	THF	45	4	33 (0)
4	DIPEA	THF	45	4	92 (8)
5	DIPEA	THF	65	2.5	96 (4)

6	DIPEA	THF	80	2	96 (4)
7	DIPEA	Toluene	65	2.5	78 (11)
8	DIPEA	CH_3CN	65	2.5	89 (11)
9	DIPEA	EtOH	65	2.5	93 (7)
10	DIPEA	Dioxane	65	2.5	90 (10)

[a] **6a** (20 mg, 0.06 mmol), base (0.12 mmol, 2 eq.), solvent (1.2 mL); [b] NMR yield.

In contrast, the hindered base *i*Pr_2NEt (DIPEA) worked well at 45 °C, providing alkene **7a** (92%) after 4 h (Table 2, entry 4) without loss of starting **6a**. Increasing the temperature to 65 °C shortened the reaction time to 2.5 h and at 80 °C this reaction was complete after 2 h (Table 2, entries 5, 6). A solvent screening showed that THF was the solvent of choice, whereas toluene and acetonitrile were less effective (Table 2, entries 7, 8).

The elimination reaction with iodides **6a-g** proceeded smoothly, affording alkenes **7a-g** (Table 1). It is also worth noting that substituted thioenol esters analogues of **7a-g** showed inhibitory activity toward *β*-amyloid production and deposition in the brain and are potential drugs for the treatment of Alzheimer's disease.[12] Thioenol esters **7a-g** reacted similarly to their oxygen analogues[6] and readily underwent rearrangement upon treatment with *t*BuOK at 0 °C to give thioketones **8** in high yields (82-95%), with the exception of two compounds with bulky *N*-1-adamantyl **8d** (20%) and *N*-*tert*-butyl **8e** (25%) groups. In the case of **7d**, decreasing the reaction temperature to -20 °C detrimentally affected the yield of **8d** (12%). It should be noted that the rearrangement of oxygen analogues containing *N*-bulky groups proceeds only *via* the decomposition pathway with the formation of *N*-(1-adamantyl)carbodiimide **3** (Scheme 1). Generally, the rearrangement reactions of thioenol esters **7a-g** proceeded faster than the oxygen analogues which can be explained by the higher reactivity of the sulfur intermediates. To quantitatively evaluate the reactivity of the thioenols we performed a kinetic study for the rearrangement of **7a** (Scheme 3, Fig. 3). Initially we tried the experiment with *t*BuOK, however even at -15 °C the reaction was completed before the NMR spectrum could be recorded. We found that utilization of LiHMDS was more convenient because the process became slow enough to record the ^{1}H NMR spectrum even at room temperature, and, moreover, the lithium salt was not precipitated from the reaction mixture.



Scheme 3. Study of the rearrangement of **7a** by ^{1}H NMR spectroscopy.

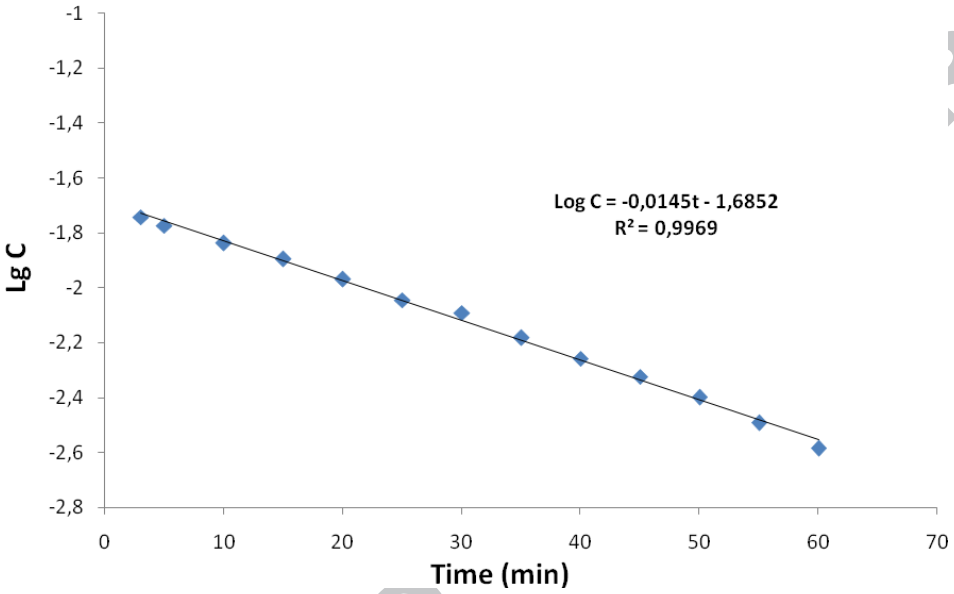
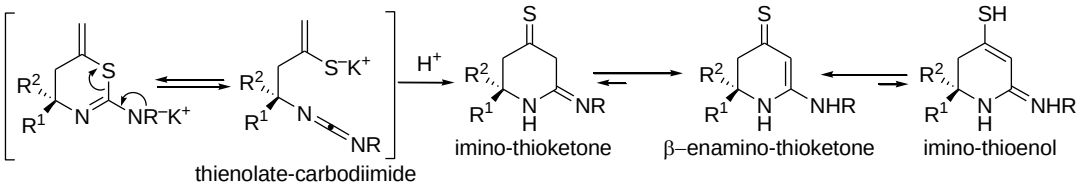


Figure 3. Kinetic curve for the rearrangement of thienol ester **7a** into thioketone **8a**.

The reaction was run in anhydrous THF at 20.5 °C and the reaction course was monitored by ^{1}H NMR spectroscopy. Based on the recorded data a kinetic curve was drawn (Fig. 3) which revealed a first-order reaction with a rate constant of 1.45×10^{-2} s^{-1} at 20.5 °C, confirming the monomolecular character of the rearrangement. The rate constant was lower than the rate constant of the enolate-isocyanate rearrangement ($k = 2.85 \times 10^{-2}$ s^{-1} at –48 °C)[11a] implying the lower reactivity of the carbodiimide group, but almost an order higher rate constant than that of the enolate-carbodiimide rearrangement ($k = 4.3 \times 10^{-3}$ s^{-1} at 20.5 °C), thus confirming the higher nucleophilicity of the thioenolate anion. We propose that the mechanism of the rearrangement is analogous to the previously described enolate-carbodiimide rearrangement (Schemes 1 and 4).



Scheme 4. Mechanism of the thioenolate-carbodiimide rearrangement and possible tautomeric products.

Deprotonation of the cyclic thioenol ester leads to ring opening with the formation of a reactive anionic thioenolate-carbodiimide which rearranges to the thioketone by ring closure *via* new C-C bond formation. The synthesized thioketones are novel compounds with unusual structures, which can be considered as cyclic conjugated analogues of thioureas. Therefore we needed additional information about the structure of **8**. The reported thioketones generally exist as enamines.[7] In our case, the NMR spectra support the same tautomeric form of **8a-g** which is analogous to the corresponding oxygen ADPs.[6] The IR spectra of powdered Bn- (**8f**) and Me-substituted (**8g**) thioketones showed strong broad signals from the hydrogen bonds at 3198-2926 cm^{-1} as well as strong bands at 1091-1007 cm^{-1} (strongest band 1054 cm^{-1}) for **8f** and 1074-1019 cm^{-1} (strongest 1074 cm^{-1}) for **8g**. In contrast to compounds **8f,g** the spectrum of **8c** (Ph-) showed no hydrogen bonds. A narrow band at 3393 cm^{-1} from the N-H bond and an intense band at 1048 cm^{-1} corresponding to the C=S bond were found.[15] The latter can be explained by the steric effect of the *N*-phenyl group in **8c** which hinders the intermolecular hydrogen bonding occurring in compounds **8f** and **8g**. Careful crystallization of a dilute solution of **8g** gave crystals suitable for single crystal X-Ray analysis, which were homochiral ($P2_12_12_1$ space group, $Z'=1$) with an absolute (*S*)-configuration, thus indicating spontaneous resolution of the racemate upon crystallization. Analysis of the molecular geometry of **8g** shows that the predominating imino-thioenol tautomer (Scheme 4) has an unusual zwitterionic structure (Fig. 4). The bond length C(2)-C(3) and C(3)-C(4) were equal to 1.432(3) and 1.359(4) Å, respectively, where the latter has higher double bond character. The distribution of bond lengths in the N(2)C(2)N(1) fragment is close to those observed for guanidine salts,[16] which can be interpreted as the presence of significant delocalization of π-density. The shortening of the N(2)-C(2) bond (1.324(3) Å) in comparison with the N(1)-C(2) bond (1.355(2) Å) and different degree of pyramidalization of the nitrogen atoms (the sum of bond angles for N(1) and N(2) atoms are 349.6 and 359.3°) match the structure of the imino-thioenol tautomer in the zwitterion form where the basic NCN fragment is protonated by an SH acidic group. In the crystal the molecule participates in an ensemble of intermolecular strong N(2)-H(2N)…S(1) hydrogen bonds (N(2)…S(1) 3.260(2) Å,

H(2N)…S(1) 2.32(4) Å, N(2)-H(2N)S(1) 170(4)°), assembling the molecules into helixes. Such distribution of bond lengths can be either an inherent characteristic of **8g** or the consequence of crystal packing effects.

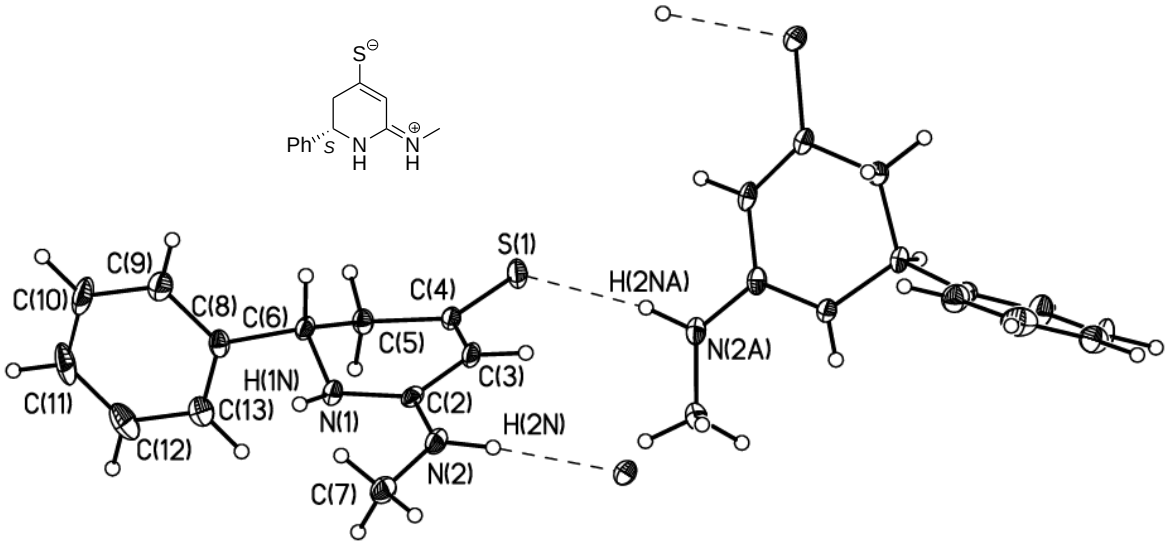
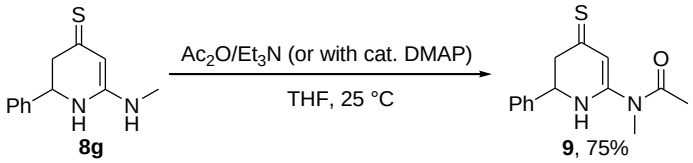


Figure 4. Fragment of the hydrogen bonded helix in (*S*)-**8g** with representation of atoms by thermal ellipsoids (p=50%).

The molecule **8g** has multiple centers available for functionalization by an electrophile *e.g.* a sulphur atom, CH= group and both nitrogens. According to the single crystal X-Ray data on electron density distribution, the most basic site is the endiamino fragment. Acetylation of **8g** with acetic anhydride (Scheme 5) was principally directed to the exocyclic nitrogen and confirmed by HSQC and HMBC spectra. About 10% of the product derived from acetylation of the cyclic nitrogen was detected and no products of acetylation on carbon or sulphur were isolated. The acetylation products are not stable and partially decomposed, even during purification.



Scheme 5. Acetylation of **8g**

The studies of other methods for the selective functionalization of these heterocycles in the context of the synthesis of biologically active compounds are currently in progress.

Conclusion

In summary, we devised a new facile and effective method for the synthesis of thioketones within a piperidine series based on thienolate-carbodiimide rearrangement. The enhanced reactivity of thioenolates allows one to consider the method not only as a new reaction, but also as a complementary tool for the construction of the 2-iminopiperidine-4-(thi)one skeleton. Compounds **8** have unusual zwitterionic structures in the solid state with guanidine type bond distribution, which requires further investigation. As noted above, thioenol esters possess high activity as potent drugs for the treatment of Alzheimer's disease and it seems to be interesting to study the same biological activity for these new thioketones.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR, IR spectra and experimental details.

Acknowledgments

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Highlights

- Synthesis of 6-amino-2,3-dihydropyridine-4-thiones without using thiophosphorus reagents
- New anionic thioenolate-carbodiimide rearrangement is disclosed
- Atom economic heterocyclic ring formation

Graphical abstract