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Base-promoted ring expansion of 3-aminopyrimidine-2-thiones into 1,2,4-triazepine-3-thiones

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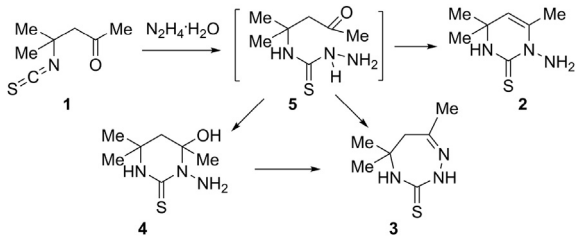
ABSTRACT

A base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones has been developed. Experimental data and DFT calculations showed that the reaction proceeded through fast formation of intermediate acyclic isomers of pyrimidines followed by their slow cyclization into triazepines. The starting hydroxypyrimidines were prepared by reaction of α,β-unsaturated ketones or β-alkoxy ketones with HNCS followed by treatment of the obtained β-isothiocyanato ketones with hydrazine. Triazepine-3-thiones were transformed into their 3-oxo analogs by oxidation with H_2O_2 under basic conditions.

1. Introduction

Rare heterocyclic scaffolds are of great interest from the viewpoint of synthetic, theoretical, and medicinal chemistry. With the exception of benzo- and hetero-fused derivatives, 1,2,4-triazepines, particularly 1,2,4-triazepin-2-ones/thiones are representative of these scaffolds.[1] Methods for the preparation of a few 1,2,4-triazepin-2-ones/thiones include reaction of arylidene ketones with $N_2H_4 \cdot 2HNCS$,[2] addition of (thio)semicarbazides to α,β-unsaturated ketones or their synthetic equivalents,[3] reaction of β-isocyanato or β-isothiocyanato ketones with hydrazines,[4,5] condensation of 1,3-dicarbonyl compounds with (thio)semicarbazides,[6] CDI-mediated cyclization of 3-hydrazino-substituted amines,[7] and reaction of thiosemicarbazides with dimethyl acetylenedicarboxylate and dibenzoyl acetylene.[8] The disadvantages of these methods are low availability of starting compounds, multistep reaction sequences, poor yields, limited synthetic flexibility, laborious procedures, etc. It should be noted that some 1,2,4-triazepin-2-ones are useful in the treatment of HIV infection.[7] However, low availability of non-fused 1,2,4-triazepin-2-ones/thiones hampers the progress of their investigation and application.

In continuation of our research into the synthesis of 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones using a ring expansion methodology,[9] we were interested in the preparation of their aza-analogs, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones and their 3-thioxo derivatives. From the literature data[2,5] we suggested that a straightforward and general approach to these heterocycles is based on the reaction of β-isothiocyanato ketones with hydrazines. This reaction was performed with 3-isothiocyanato-1,3-diphenylpropan-1-one,[5b,c] 2-(1-isothiocyanatocyclopentyl)cyclopentanone,[5c,d] and the readily available 4-isothiocyanato-4-methylpentan-2-one[5d,e] (**1**, Scheme 1) under neutral, acidic, or basic conditions.



Scheme 1. Reaction of isothiocyanate **1** with hydrazine.

It was demonstrated that isothiocyanate **1** reacts with hydrazine hydrate under heating in water in the presence of mineral acid to yield pyrimidine derivative **2** (Scheme 1).[10] Later it was reported that the product of this reaction is not the pyrimidine **2** but triazepine **3** which can also be prepared by reaction of isothiocyanate **1** with hydrazine hydrate in refluxing benzene using a Dean–Stark trap.[5e] In contrast, under the given conditions[5e,10] we obtained 3-

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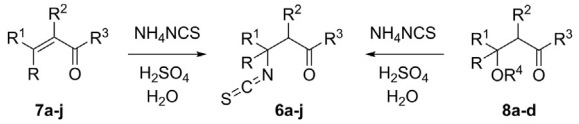
aminopyrimidine-2-thione **4** as the major compound, and the amount of triazepinethione **3** did not exceed 5% and 15%, respectively (according to ^{1}H NMR spectra of the isolated crude products). This indicates that rapid cyclization of the intermediate thiosemicarbazide **5** into pyrimidine derivative **4** is followed by its slow transformation into triazepinethione **3** via ring expansion with nitrogen insertion. Therefore, results of the reaction of isothiocyanato ketones with hydrazines do not appear to be so clear as reported previously.[2,5,10] Indeed, the initially formed 4-(γ-oxoalkyl) thiosemicarbazides (e.g., **5**) can undergo various transformations, including cyclization into 1,2,4-triazepine-3-thiones, derivatives of pyrimidine, fused heterocyclic systems, macrocyclic compounds, etc.[11]

Based on the reported data and our experience, we hypothesized that 3-amino-4-hydroxyhexahydropyrimidine-2-thiones obtained by the reaction of β-isothiocyanato ketones with hydrazines can serve as starting compounds for the preparation of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones. Here, we report the synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones by base-promoted ring expansion of 3-amino-4-hydroxyhexahydropyrimidine-2-thiones, a plausible pathway of this transformation based on experimental data and DFT calculations, and oxidative transformation of the obtained 1,2,4-triazepine-3-thiones into the corresponding 3-oxo derivatives. Two preparative procedures for the synthesis of β-isothiocyanato ketones are also reported.

2. Results and discussion

2.1. Synthesis of starting β-isothiocyanato carbonyl compounds

Preparation of β-isothiocyanato aldehydes and ketones was the first step of the triazepine synthesis. These isothiocyanates have been the focus of considerable attention since 1946,[12] and they have found a broad application as versatile precursors in organic synthesis.[13] The most general and straightforward preparative route to these compounds involves the addition of HNCS generated by treatment of thiocyanate salts with strong mineral acids to α,β-unsaturated aldehydes and ketones in water.[14–16] Success of this reaction is highly dependent on the substrate structure, particularly on the nature of the substituents.[14,15b] Therefore, in each particular case, careful optimization of reaction conditions should be carried out. As a consequence it is not surprising that the number of β-isothiocyanato aldehydes and ketones described still remains somewhat limited. For the present study, isothiocyanates **6a**–**j** were chosen as a starting material (Scheme 2, Table 1). Among them, only compounds **6a**,**j** could be considered to be synthetically available. As for other isothiocyanates, their synthesis was either not reported previously (for **6d**,**h**,**i**),[17,25] or they were obtained only as crude products (for **6e**–**g**),[5a,18,19] or procedures for their preparation were far from optimal (for **6b**,**c**).[15b,20]



Scheme 2. Synthesis of β-isothiocyanato carbonyl compounds **6a**–**j**.

Two alternative methods were used for the synthesis of starting isothiocyanates **6a**–**j**. The first method was based on the addition of HNCS to unsaturated carbonyl compounds **7a**–**j**, and the second was our original method involving the reaction of HNCS with β-alkoxy ketones **8a**–**d** (Scheme 2).

β-Alkoxy ketones **8a**–**d** were prepared by directed aldol type condensation of TMS ethers of acetone, cyclopentanone, or cyclohexanone with acetone dimethyl acetal or acetaldehyde diethyl acetal in the presence of $ZnCl_2$ in AcOEt.[21] During the reaction and vacuum distillation, β-alkoxy ketones **8a**–**c** partly converted into the corresponding unsaturated ketones **7b**,**d**,**h**. Compounds **6a**–**j** were synthesized by reacting **7a**–**j**, **8d** or mixtures of **7b**,**d**,**h** and **8a**–**c** with NH_4SCN in the presence of H_2SO_4 in water. The ratio of the reagents, the reaction temperature and time were optimized to achieve maximum conversion of starting compounds (92–100% according to ^{1}H NMR spectra of the crude products) (Table 1).

Under improved reaction conditions mesityl oxide (**7a**) reacted with HNCS (1.05 equiv) for 15 min upon heating at 70–80 °C to give isothiocyanate **6a** in 75% isolated yield (Table 1, entry 1). Isothiocyanato ketones **6b**–**e**,**h**,**i** were prepared using a greater excess of HNCS (1.96–3.01 equiv) and heating at 60 °C for 3–7 h (entries 2–5, 8, and 9). The same temperature was used for the preparation of isothiocyanate **6g** from ketone **7g** (entry 7). In contrast, the addition of HNCS to ketone **7f** smoothly proceeded at 5 °C for 25 h (entry 6). The amount of isothiocyanate **6f** in the isolated crude product significantly decreased within the reaction temperature range of 20–90 °C (^{1}H NMR spectroscopic data). Mild reaction conditions were applied for the synthesis of isothiocyanate **6j** from aldehyde **7j** (entry 10). Compounds **6c**,**d**,**g**,**h** with two stereocenters formed as diastereomeric mixtures (Table 1). The isothiocyanates **6a**–**j** obtained were purified by vacuum distillation. Partial elimination of HNCS proceeded during distillation of **6d**,**e**,**f**,**h** to give an admixture of the corresponding unsaturated ketone **7d**,**e**,**f**,**h** (3–21%) in the resulting product. The amount of this admixture was taken into account in the following synthetic step.

Table 1
Optimized reaction conditions for the synthesis of β-isothiocyanato carbonyl compounds **6a**–**j**.[a]

Entry	**7** or/and **8** (**7**/**8** ratio)	Reagents ratio[b]	R	R^1	R^2	R^3	R^4	Temp (°C)[c]	Time (h)	**6**	Yield (%)[d]	Isomer ratio[e]
1	**7a**	1.05:0.53:1	Me	Me	H	Me	—	70–80	0.25	**6a**	75	—
2	**7b**+**8a** (3:97)	2.03:1.02:1	Me	H	H	Me	OEt	60	3	**6b**	81	—
3	**7c**	2.53:1.27:1	Me	H	Me	Me	—	60	4	**6c**	86	60:40
4	**7d**+**8b** (55:45)	2.11:1.06:1	Me	H	$CH_2CH_2CH_2$		OEt	60	4	**6d**	74	70:30
5	**7e**	3.01:1.51:1	Me	Me	$CH_2CH_2CH_2$		—	60	7	**6e**	74	—
6	**7f**	2.50:1.25:1	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$		—	5	25	**6f**	62	—
7	**7g**	1.05:1.05:1	H	$CH_2CH_2CH_2CH_2$		Me	—	60	4	**6g**	59	56:44
8	**7h**+**8c** (13:87)	1.96:0.98:1	Me	H	$CH_2CH_2CH_2CH_2$		OEt	60	3	**6h**	90	63:37
9	**8d**	2.05:1.02:1	Me	Me	$CH_2CH_2CH_2CH_2$		OMe	60	3	**6i**	90	—
10	**7j**	1.41:0.71:1	Me	H	H	H	—	rt, then 40	1, then 1	**6j**	56	—

[a] Level of conversion of the starting material is 100% (entries 1, 2, 8–10), 96% (entry 3), 95% (entries 4, 5), and 92% (entry 6).
[b] NH_4SCN/H_2SO_4/substrate molar ratio.
[c] Bath temperature.
[d] Isolated yield (after vacuum distillation).
[e] After vacuum distillation.