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ORIGINAL PAPER

# A selective synthesis of β-isothiocyanato ketones through a Staudinger/aza-Wittig reaction of β-azido ketones

**Anastasia A. Fesenko · Ekaterina A. Dem'yachenko · Galina A. Fedorova · Anatoly D. Shutalev**

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**Abstract** A novel selective two-step synthesis of β-isothiocyanato ketones from α,β-unsaturated ketones has been developed. The synthesis includes preparation of β-azido ketones followed by reaction with triphenylphosphine and carbon disulfide. Treatment of the obtained β-isothiocyanato ketones with ammonia or methylamine gives corresponding hexahydro-4-hydroxypyrimidine-2-thiones. The latter are also prepared directly from β-azido ketones without isolation of the intermediate β-isothiocyanato ketones.

**Keywords** Azides · Isothiocyanates · Carbonyl compounds · Phosphorus compounds · Three-component reaction · Pyrimidines

## Introduction

β-Isothiocyanato aldehydes and ketones (e.g., **1**), possessing two reactive functional groups, have proved to be versatile starting materials for the synthesis of a wide range of nitrogen-containing acyclic and heterocyclic compounds. Since the first representatives of **1** have been described in 1946 [1], their chemistry was extensively studied [2, 3]. They were used in preparation of various pyrimidines [4–6], 1,3-thiazines [7, 8], 1,3-oxazines [9], pyridines [10], nucleosides [11, 12], pyrroles [13], 1,2,4-triazepines [14], condensed heterocycles [15–17], etc.

A. A. Fesenko · E. A. Dem'yachenko · G. A. Fedorova · A. D. Shutalev (✉)
Department of Organic Chemistry, Moscow State University of Fine Chemical Technologies, Moscow, Russian Federation
e-mail: shutalev@orc.ru

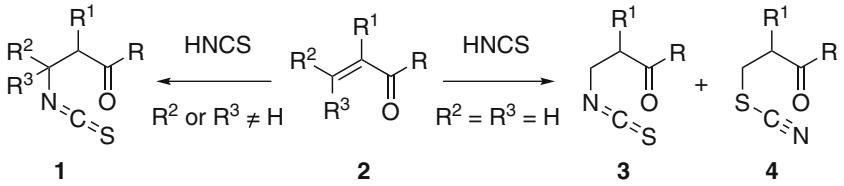
The most commonly used synthesis of β-isothiocyanato aldehydes and ketones **1** involves the addition of thiocyanic acid to the corresponding α,β-unsaturated carbonyl compounds **2** (Scheme 1) [1, 18, 19]. However, reaction of β-unsubstituted α,β-unsaturated aldehydes or ketones (**2**, $R^2 = R^3 = H$) with thiocyanic acid proceeds with low selectivity, resulting in mixtures of isomeric β-isothiocyanates **3** and β-thiocyanates **4** (up to 50 %) [20, 21], which are difficult to separate because of similar physical properties. This drawback confines the use of β-unsubstituted β-isothiocyanato aldehydes and ketones in organic synthesis.

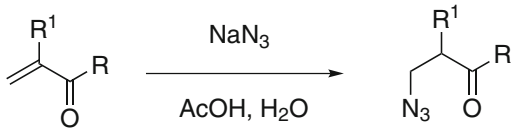
We hypothesized that α,β-unsaturated aldehydes and ketones could be selectively transformed into respective β-isothiocyanato carbonyl compounds **1** and **3** by the addition of $HN_3$ to give β-azido aldehydes and ketones [22, 23] followed by transformation of the azido group into an isothiocyanato group using a Staudinger/aza-Wittig sequence [24–30]. In our preliminary communication, an example of the application of this methodology has been described [31]. Herein, we report full details of the selective synthesis of β-unsubstituted β-isothiocyanato ketones from α,β-unsaturated ketones. We also describe further transformation of the obtained isothiocyanates into hardly accessible 6-unsubstituted hexahydro-4-hydroxypyrimidine-2-thiones in high yields.

## Results and discussion

Starting β-azido ketones **5a** and 5**b** were prepared according to the literature procedure based on the reaction of methyl vinyl ketone (**6a**) and isopropenyl methyl ketone (**6b**) with sodium azide in aqueous acetic acid at room temperature (Scheme 2) [23]. β-Azido ketone **5c** was first synthesized following this procedure from phenyl vinyl

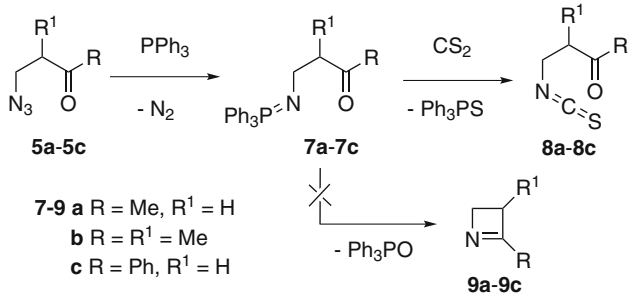
**Scheme 1**




**5**, **6 a** R = Me, $R^1$ = H; **b** R = $R^1$ = Me; **c** R = Ph, $R^1$ = H

**Scheme 2**




**Scheme 3**

ketone (**6c**). Previously, compound **5c** was obtained by reaction of 3-chloro-1-phenylpropan-2-one with sodium azide [32] or treatment of 1-phenylcyclopropanol with sodium azide in the presence of cerium (IV) ammonium nitrate [33].

Azides **5a**–**5c** were isolated from reaction mixtures as yellowish oils in 62–88 % yields after extraction with diethyl ether followed by neutralization of ether extracts with aqueous $Na_2CO_3$, drying and evaporation of solvent in vacuum. The purity of the crude **5a**–**5c** was excellent (>95 % according to $^1$H NMR data), and they were used in further transformations without additional purification.

First, transformation of the azido group of compounds **5a**–**5c** into an isothiocyanato group was examined using azide **5a** as a starting material. After treatment of this compound with one equivalent of triphenylphosphine in dry THF at room temperature, nitrogen evolution via the Staudinger reaction was observed. Subsequent addition of excess of carbon disulfide to the obtained solution of iminophosphorane **7a** gave the target isothiocyanate **8a** (Scheme 3). The latter was isolated after solvent removal and extraction of the residue with a petroleum ether–diethyl ether mixture (1:1). However, the yield of **8a** did not exceed 30 %.

A more convenient procedure of synthesis of **8a** involved treatment of a solution of **5a** in THF-$CS_2$ with triphenylphosphine at room temperature for several hours. Yield of **8a** increased when after cessation of nitrogen evolution, the reaction mixture was refluxed for 1–1.5 h. Under optimal conditions (THF-$CS_2$, rt, 1.5 h, then reflux, 1 h), the yield of oily **8a** from azide **5a** was 53 % after vacuum distillation. Oily isothiocyanate **8b** and solid isothiocyanate **8c** were prepared analogously from azides **5b** and **5c** in 82 and 52 % yields, respectively. Notably, the products of intramolecular aza-Wittig reaction of iminophosphoranes **7a**–**7c**, azetines **9a**–**9c**, were not detected in the studied reactions. Previously, Eguchi et al. [34] reported the formation of 2-phenyl-1-azetine (**9c**) by the reaction of **5c** with $PPh_3$, however, in very low yield.

The reactions between azides **5a**, **5c** and triphenylphosphine (1 equiv.) with or without carbon disulfide in $CDCl_3$ were monitored by $^1$H and $^{13}$C NMR spectroscopy at 25 °C. According to the $^1$H NMR spectroscopy data (Table 1, Fig. 1), the reaction of **5a** with $PPh_3$ in $CDCl_3$ was complete within 1.5 h to give iminophosphorane **7a** and methyl vinyl ketone (**6a**) in a 62:33 ratio, respectively. Ketone **6a** probably resulted from base-promoted elimination of hydrazoic acid from **5a** under the action of **7a**. Strong basic properties of iminophosphoranes are well documented in the literature [24–29]. The formation of azetine **9a** was not detected in the NMR experiment.

The structure of iminophosphorane **7a** was confirmed by its $^1$H and $^{13}$C NMR spectra. Thus, the $^1$H NMR spectrum of **7a** showed a singlet at 2.14 ppm because of the methyl group, a doublet of triplets at 3.24 ppm ($^3J$ = 6.7 and $^3J_{H,P}$ = 10.1 Hz) and a triplet at 2.97 ppm ($^3J$ = 6.7 Hz) assigned to the methylene groups of N–$CH_2$–$CH_2$ fragment. In the $^{13}$C NMR spectrum the signals of the $CH_2$–$CH_2$–C(O)–$CH_3$ moiety were observed at 45.0 (*d*, $^2J_{C,P}$ = 11.6 Hz), 38.1 (*d*, $^3J_{C,P}$ = 2.2 Hz), 207.7 (*s*) and 30.2 (*s*) ppm, respectively.

Table 2 and Fig. 2 show the $^1$H NMR monitoring data for the reaction between **5a**, $PPh_3$ (1 equiv.) and $CS_2$ at 25 °C in a mixture of $CDCl_3$–$CS_2$. Under these conditions, the rate of the formation of compound **8a** was rather low. After 39 min, azide **5a**, isothiocyanate **8a**, iminophosphorane **7a** and methyl vinyl ketone **6a** in a 38:45:10:7 ratio were observed. After 4 h, the amount of isothiocyanate **8a** increased to 62 %. Two unidentified products (or intermediates) were also formed in the reaction; however, the overall amount of these products did not exceed 15 %.

**Table 1** Reaction of **5a** with $PPh_3$ ($CDCl_3$, 25 °C): dependence of the product distribution on the reaction time

| Time/min | Product distribution/% | | |
|---|---|---|---|
| | **5a** | **7a** | **6a** |
| 3 | 85 | 14 | 1 |
| 12 | 62 | 28 | 10 |
| 16 | 49 | 36 | 15 |
| 26 | 34 | 45 | 21 |
| 36 | 24 | 50 | 26 |
| 46 | 16 | 54 | 30 |
| 56 | 12 | 57 | 31 |
| 66 | 9 | 58 | 33 |
| 76 | 7 | 61 | 32 |
| 86 | 6 | 61 | 33 |
| 96 | 5 | 62 | 33 |

A solution of 60.7 mg $PPh_3$ (0.231 mmol) in 0.5 $cm^3$ $CDCl_3$ was added at once to a 5-mm NMR tube charged with 26.2 mg **5a** (0.232 mmol). The solution obtained was shaken carefully (gas evolution!). The progress of the reaction was monitored by $^1H$ NMR spectroscopy

Similar results as described for **5a** were obtained from NMR studies of the reactions between **5c** and $PPh_3$ with or without $CS_2$ in $CDCl_3$.

Compared with the literature method [1–3, 18, 19], the above-described two-step methodology allows obtaining β-unsubstituted β-isothiocyanato ketones from α,β-unsaturated ketones with full chemoselectivity. The prepared isothiocyanates **8a**–**8c** were free from the corresponding isomeric thiocyanates **4**, whereas the previously described **8a**, **8b** [35] were mixtures of the β-isothiocyanato and β-thiocyanato ketones in ratios of 50:50 and 65:35, respectively [21].

One of the most important reactions of β-isothiocyanato ketones and aldehydes is that with ammonia or primary amines to provide hexahydro-4-hydroxypyrimidine-2-thiones or products of their further transformations generally in good yields [2–6]. These compounds are currently of great interest because of their remarkable biological activities [36–38] and versatile synthetic applications [5, 8, 10, 39–42]. However, the previously described reactions of compounds **8a**, **8b** with ammonia and amines afforded the products in rather low yields. For example, treatment of **8a** with ammonia in ethanol gave 1,2,3,4-tetrahydro-6-methylpyrimidine-2-thione in only 40 % yield [43]. The reaction of **8a** with ammonia in diethyl ether afforded hexahydro-4-methoxy-4-methylpyrimidine-2-thione in 18 % yield after silica gel column chromatography of the obtained

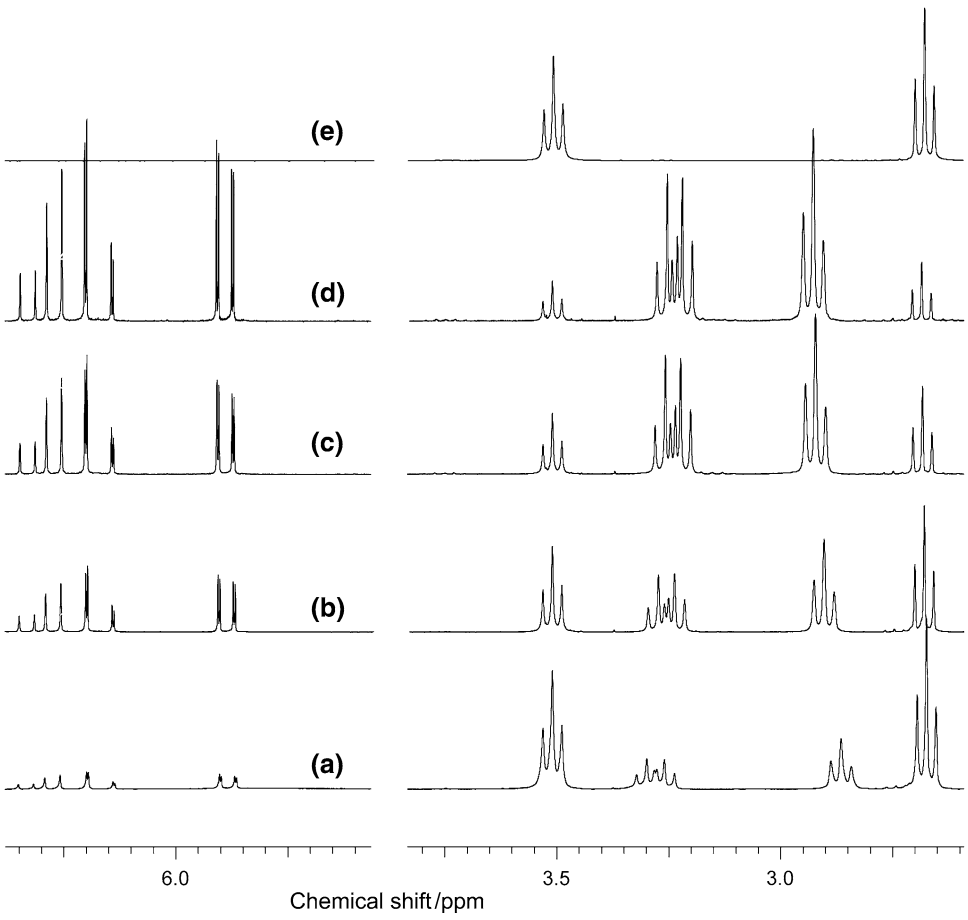



**Fig. 1** **a**–**d** $^1H$ NMR spectra for the reaction of **5a** with $PPh_3$ ($CDCl_3$, 25 °C) after 12, 26, 46 and 66 min, respectively; **e** $^1H$ NMR spectra of **5a** in $CDCl_3$

**Table 2** Reaction of **5a** with $PPh_3$ and $CS_2$ ($CDCl_3$, 25 °C): dependence of the product distribution on the reaction time

| Time/min | Product distribution/% | | | |
|---|---|---|---|---|
| | **5a** | **8a** | **7a** | **6a** |
| 6 | 83 | 11 | 5 | 1 |
| 10 | 69 | 21 | 7 | 3 |
| 15 | 60 | 28 | 8 | 4 |
| 39 | 38 | 45 | 10 | 7 |
| 77 | 27 | 54 | 11 | 8 |
| 254 | 18 | 62 | 12 | 8 |
| 372 | 18 | 63 | 11 | 8 |

A solution of 81.1 mg $PPh_3$ (0.309 mmol) in 0.3 $cm^3$ $CDCl_3$ was added at once to a 5-mm NMR tube charged with a solution of 34.2 mg **5a** (0.302 mmol) in 0.3 $cm^3$ $CS_2$. The solution obtained was shaken carefully (gas evolution!). The progress of the reaction was monitored by $^1H$ NMR spectroscopy

product using an ethyl acetate-methanol mixture as eluent [42]. Isothiocyanate **8a** reacted with methylamine in water to give acyclic *N*-methyl-*N*'-(3-oxobut-1-yl)thiourea in 10 % yield [44]. Obviously, the low purity of the starting isothiocyanates, because of the presence of considerable amounts of the isomeric thiocyanates, explains these poor yields. Thus, with the aim of developing a preparative synthesis of 6-unsubstituted hexahydro-4-hydroxypyrimidine-2-thiones, we studied the reaction of pure isothiocyanates **8a**, **8b** with ammonia and methylamine.

Prepared following our procedure, compounds **8a**, **8b** readily reacted with concentrated aqueous ammonia (1.5 equiv.) in MeCN at room temperature for 1–1.5 h to provide the corresponding hydroxypyrimidines **10a**, **10b** in 78 and 89 % yields, respectively. Similarly, reaction of **8a** with concentrated aqueous methylamine (MeCN, rt, 1.5 h) gave pyrimidine **10c** in 82 % yield (Scheme 4).

Hydroxypyrimidines **10a**, **10b**, **10d** were conveniently synthesized directly from azido ketones **5a**, **5b** without purification of the intermediate isothiocyanates **8a**, **8b**. Thus, the reaction of azide **5b** with $PPh_3$–$CS_2$ in THF followed by evaporation of solvent and extraction of the residue with petroleum ether–diethyl ether mixture (1:1) gave a solution of crude isothiocyanate **8b**. Removal of solvent in vacuum, treatment of the residue with concentrated aqueous ammonia or methylamine in MeCN at room temperature, followed by evaporation of solvent and treatment of the solid residue with diethyl ether afforded chromatographically and spectroscopically pure hydroxypyrimidines **10b**, **10d** in 84 and 73 % overall yields, respectively. This procedure was also used for the synthesis of hydroxypyrimidine **10a** from azide **5a** in 59 % overall yield.

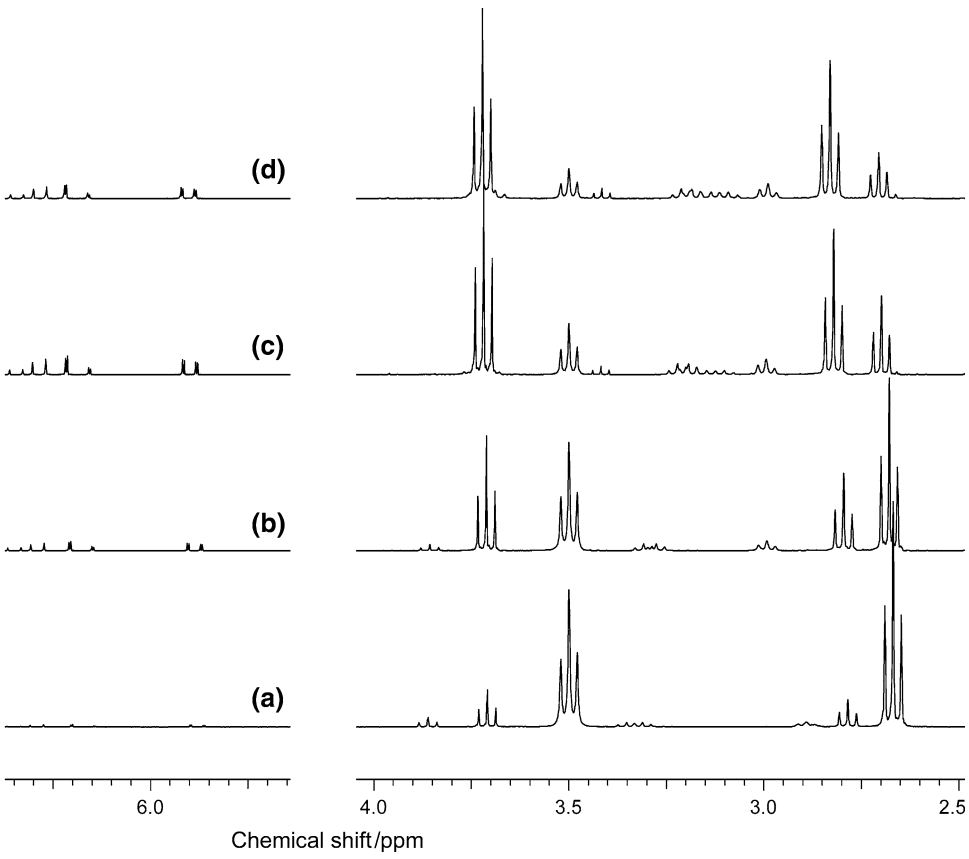
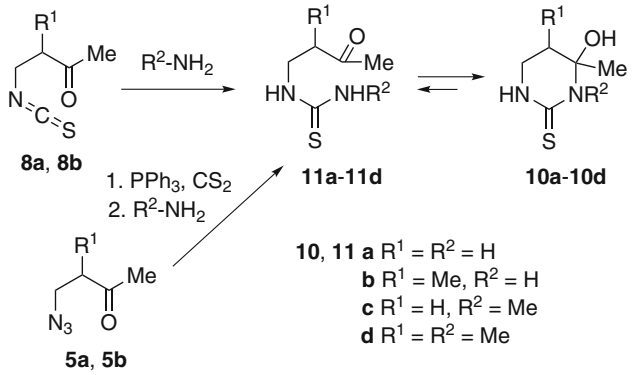



**Fig. 2** **a–d** $^1H$ NMR spectra for the reaction of **5a** with $PPh_3$ and $CS_2$ ($CDCl_3$, 25 °C) after 6, 15, 77 and 254 min, respectively




**Scheme 4**

According to IR spectroscopic data, all the obtained pyrimidines **10a**–**10d** exist exclusively in the cyclic form in the solid state. These forms were also observed in $^{1}$H and $^{13}$C NMR spectra immediately after dissolution of **10a**–**10d** in DMSO-$d_6$.

$^{1}$H NMR spectra showed that **10b**, **10d** were obtained as mixtures of (4*R**, 5*R**) and (4*R**, 5*S**)-diastereomers with overwhelming predominance of the former isomer (94:6 and 99.5:0.5 for **10b** and **10d**, respectively). In DMSO-$d_6$ solutions, the major isomers adopted a conformation with an axial orientation of the hydroxyl group and equatorial orientation of the 5-Me group. It was confirmed by the presence of the long range coupling constant $^{4}J_{OH,5\text{-}H} = 0.4$–$0.6$ Hz because of a W-shaped arrangement of the OH and 5-H protons and the high value of the vicinal coupling between 5-H and axial 6-H (for **10d**). The long range coupling $^{4}J_{OH,\ 5\text{-}H} = 0.3$–$0.8$ Hz was also observed in $^{1}$H NMR spectra of pyrimidines **10a**, **10c** in DMSO-$d_6$, proving an axial orientation of the hydroxyl group in these compounds.

According to $^{1}$H NMR spectra, the *N*-unsubstituted pyrimidines **10a**, **10b** remained in cyclic form in DMSO-$d_6$ solutions at room temperature for a prolonged time; however, their slow dehydration was observed. For example, after 9 days, pyrimidine **10a** converted into a mixture of **10a**, 1,2,3,4-tetrahydro-6-methylpyrimidine-2-thione (**12a**) and hexahydro-4-methylenepyrimidine-2-thione (**13a**) in a 85:10:5 ratio. After 2 and 9 days, (4*R**, 5*R**)-**10b** transformed into mixtures of (4*R**, 5*R**)-**10b**, (4*R**, 5*S**)-**10b**, 1,2,3,4-tetrahydro-5,6-dimethylpyrimidine-2-thione (**12b**) and hexahydro-5-methyl-4-methylenepyrimidine-2-thione (**13b**) in ratios of 70:20:8:2 and 6:2:89:3, respectively. In contrast to **10a**, **10b**, *N*-methyl-substituted pyrimidines **10c**, **10d** in DMSO-$d_6$ solutions at room temperature slowly gave equilibrium mixtures of **10c**, **10d** and their acyclic isomers **11c**, **11d**. For example, after 14 days, the $^{1}$H NMR spectrum of **10c** showed a 58:42 mixture of **10c** and **11c**. After 2, 7, 9 and 21 days, **10d** transformed into mixtures of (4*R**, 5*R**)-**10d**, (4*R**, 5*S**)-**10d** and **11d** in ratios of 84:7:9, 75:10:15, 72:11:17 and 61:14:25, respectively.

In summary, a novel chemoselective two-step approach to β-isothiocyanato ketones starting from α,β-unsaturated ketones was developed. The synthesis involved preparation of β-azido ketones followed by reaction with triphenylphosphine and carbon disulfide. This approach was especially useful for synthesis of β-unsubstituted β-isothiocyanato ketones, which cannot be prepared with sufficient purity by commonly used procedures. Treatment of the obtained β-isothiocyanato ketones with ammonia or methylamine gave corresponding 6-unsubstituted hexahydro-4-hydroxypyrimidine-2-thiones in high yields. These heterocycles were also prepared directly from β-azido ketones without intermediate purification of the β-isothiocyanato ketones.

## Experimental

FT IR spectra were recorded using a Bruker Vector 22 spectrophotometer in Nujol for solid samples or in film for liquid samples. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w) and shoulder (sh). $^{1}$H and proton-decoupled $^{13}$C NMR spectra (solutions in DMSO-$d_6$ or $CDCl_3$) were acquired using a Bruker DPX 300 spectrometer at 300.13 MHz ($^{1}$H) and 75.48 MHz ($^{13}$C). $^{1}$H NMR chemical shifts are referenced to the residual proton signal in DMSO-$d_6$ (2.50 ppm) or $CDCl_3$ (7.25 ppm). In $^{13}$C NMR spectra, central signals of DMSO-$d_6$ (39.50 ppm) or $CDCl_3$ (77.00 ppm) were used as references. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) and some combinations of these, multiplet (m). Selective $^{1}$H-$^{1}$H decoupling and DEPT-135 experiments were used to aid in the assignment of $^{1}$H and $^{13}$C NMR signals. Elemental analyses (CHN) were performed by using a Thermo Finnigan Flash EA1112 apparatus. The results were found to be in good agreement (±0.3 %) with the calculated values. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 $F_{254}$ aluminum-backed plates in chloroform–methanol (9:1, v/v) and chloroform–methanol (5:1, v/v) as solvent systems. Spots were visualized with iodine vapors or UV light. Column chromatography was performed with Merck silica gel 60 (0.04–0.063 mm).

THF was dried over KOH pellets and then over Na-benzophenone followed by distillation. All other reagents and solvents were purchased from commercial sources and used without further treatment. β-Azido ketones **5a**, **5b** were prepared according to the literature procedure [23] as yellowish oils with high purity in 62–63 % yields by reaction of ketones **6a**, **6b** with $NaN_3$ in aqueous acetic acid at room temperature followed by extraction with

diethyl ether, neutralization with 7 % aqueous $Na_2CO_3$, drying over $MgSO_4$, filtration and removal of solvent in vacuum. Azides **5a**, **5b** were used in further transformations without additional purification.

*3-Azido-1-phenylpropan-1-one* (**5c**)

To a stirred solution of 8.467 g vinyl phenyl ketone (**6c**, 64.07 mmol) in 70 $cm^3$ AcOH was added dropwise a solution of 12.504 g $NaN_3$ (192.34 mmol) in 50 $cm^3$ $H_2O$ over 25 min at room temperature. The reaction mixture was stirred for 4 h at room temperature and extracted with diethyl ether (2 × 50 $cm^3$ and 2 × 30 $cm^3$). The combined ether extracts were subsequently washed with 7 % aqueous solution of $Na_2CO_3$ (to pH 9), water (to pH 7), brine and dried over $MgSO_4$. [Caution: generated hydrazoic acid ($HN_3$) is a very volatile, highly toxic and explosive compound. All operations involving hydrazoic acid should be carried out in an efficient fume hood following appropriate precautions]. The solvent was removed in vacuum to give 9.882 g (88 %) **5c** as yellowish oil. According to $^1$H NMR analysis, the purity of the crude **5c** was excellent, and it was used in further transformations without additional purification. The $^1$H NMR spectrum of the product is essentially identical with the $CDCl_3$ spectrum of this compound described in Ref. [33].

*4-Isothiocyanatobutan-2-one* (**8a**, $C_5H_7NOS$)

To a cooled ice bath a stirred solution of 3.650 g 4-azidobutan-2-one (**5a**, 32.27 mmol) in 31 $cm^3$ dry THF and 6 $cm^3$ $CS_2$ was added 8.463 g $PPh_3$ (32.27 mmol) (caution: vigorous evolution of nitrogen). The resulting solution was stirred for 2.5 h at room temperature cooled ice bath a stirred solution and the solvent was removed in vacuum. The residue was triturated with 10 $cm^3$ diethyl ether–petroleum ether mixture (1:1 v/v) until crystallization was complete; the precipitate was filtered and washed with diethyl ether–petroleum ether mixture (3 × 5 $cm^3$, 1:1 v/v). The organic phases were combined, the solvent was removed in vacuum, and the oily residue, containing **8a** and a small amount of $Ph_3PS$, was distilled in vacuum to give 2.656 g (64 %) **8a** as a slightly yellow oil. A small amount of **8a** was also purified by column chromatography on silica gel eluting with $CHCl_3$–hexane mixtures (from 1:50 to 1:10) and then with $CHCl_3$. B.p.: 88–90 °C (0.13 mbar); $n_D^{20} = 1.5193$; $^1$H NMR ($CDCl_3$): $\delta = 3.73$ (*t*, $^3J = 6.5$ Hz, 2H, $CH_2N$), 2.81 (*t*, $^3J = 6.5$ Hz, 2H, $CH_2C{=}O$), 2.17 (*s*, 3H, $CH_3$) ppm; $^{13}$C NMR ($CDCl_3$): $\delta = 204.24$ (C=O), 130.80 (N=C=S), 42.59 ($CH_2C{=}O$), 39.34 ($CH_2N$), 29.97 ($CH_3$) ppm; IR (film): $\bar{\nu} = 2{,}196$ *s*, 2,121 *vs* (ν N=C=S), 1,719 *s* (ν C=O)/cm.

*4-Isothiocyanato-3-methylbutan-2-one* (**8b**, $C_6H_9NOS$)

To a cooled ice bath a stirred solution of 16.30 g 4-azido-3-methylbutan-2-one (**5b**, 0.128 mol) in 70 $cm^3$ $CS_2$ was added dropwise over a period of 40 min a solution of 36.98 g $PPh_3$ (0.141 mol) in 60 $cm^3$ dry THF. The reaction mixture was stirred for 2.3 h, while the temperature was maintained at about 20 °C using a water bath. Then the mixture was refluxed for 1 h and the solvent was removed in vacuum. The residue was triturated with 40 $cm^3$ diethyl ether-petroleum ether mixture (1:1 v/v) until crystallization was complete; the precipitate was filtered and washed with diethyl ether–petroleum ether mixture (3 × 12 $cm^3$, 1:1 v/v). The organic phases were combined, the solvent was removed in vacuum, and the oily residue, containing **8b** and a small amount of $Ph_3PS$, was distilled in vacuum to give 15.06 g (82 %) **8b** as a slightly yellow oil. B.p.: 89.5–92 °C (0.13 mbar); $n_D^{20} = 1.5150$; $^1$H NMR ($CDCl_3$): $\delta = 3.74$ (*dd*, $^2J = 14.3$, $^3J = 6.5$ Hz, 1H, CH(A) in $CH_2N$), 3.53 (*dd*, $^2J = 14.3$, $^3J = 6.5$ Hz, 1H, CH(B) in $CH_2N$), 2.86 (*tq*, $^3J = 7.3$, $^3J = 6.5$, $^3J = 6.5$ Hz, 1H, CHC=O), 2.21 (*s*, 3H, $CH_3C{=}O$), 1.22 (*d*, $^3J = 7.3$ Hz, 3H, $CH_3CH$) ppm; $^{13}$C NMR ($CDCl_3$): $\delta = 208.24$ (C=O), 131.23 (N=C=S), 46.83 (CHC=O), 46.30 ($CH_2N$), 28.51 ($CH_3C{=}O$), 14.45 ($CH_3CH$) ppm.

*3-Isothiocyanato-1-phenylpropan-1-one* (**8c**, $C_{10}H_9NOS$)

To a cooled ice bath a stirred solution of 1.634 g 3-azido-1-phenylpropan-2-one (**5c**, 9.33 mmol) in 6 $cm^3$ $CS_2$ and 9 $cm^3$ dry THF was added 2.508 g $PPh_3$ (9.56 mmol). The reaction mixture was stirred for 1.5 h at room temperature and refluxed for 4 h, and the solvent was removed in vacuum. The residue was triturated with 6 $cm^3$ acetone–petroleum ether mixture (8:5 v/v) until crystallization was complete and cooled; the precipitate was filtered and washed with an acetone–petroleum ether mixture (2 × 2 $cm^3$, 8:5 v/v). The organic phases were combined and the solvent was removed in vacuum. The residue was extracted with diethyl ether (5 × 5 $cm^3$), the solvent was removed, and the residue was extracted with boiling hexane (5 × 15 $cm^3$). The aim of these subsequent extractions was to remove $Ph_3PS$ as completely as possible without loss of **8c**; the extraction with boiling hexane removed the yellow coloring of the raw material. After evaporation of hexane, the product was crystallized from $CHCl_3$–hexane mixture (1:4 v/v) to give 0.910 g (51 %) **8c** as a white solid. (Note: syntheses of **8c** using more than 3 g of starting material **5c** are not recommended because the workup becomes laborious). M.p.: 73.5–74 °C ($CHCl_3$–hexane, 1:4 v/v); $^1$H NMR (DMSO-$d_6$): $\delta = 7.97$–$8.02$ (*m*, 2H, $C_{(2)}H$ and $C_{(6)}H$ in Ph), 7.64–7.71 (*m*, 1H, $C_{(4)}H$ in Ph), 7.52–7.59 (*m*, 2H,

$C_{(3)}H$ and $C_{(5)}H$ in Ph), 3.99 (*t*, $^3J = 6.2$ Hz, 2H, $CH_2N$), 3.54 (*t*, $^3J = 6.2$ Hz, 2H, $CH_2C{=}O$) ppm; $^{13}C$ NMR (DMSO-$d_6$): $\delta = 196.81$ (C=O), 135.93 ($C_{quat}$ in Ph), 133.62 ($C_{para}$ in Ph), 128.80 ($C_{ortho}$ in Ph), 128.01 ($C_{meta}$ in Ph), 127.33 (N=C=S), 39.91 ($CH_2N$), 37.78 ($CH_2C{=}O$) ppm; IR (Nujol): $\bar{\nu} = 2{,}206$ *s*, 2,125 *vs* (ν N=C=S), 1,675 *s* (ν C=O), 1,591 *m* (ν CC in Ph), 752 *s*, 691 *s* (δ CH in Ph)/cm.

*Hexahydro-4-hydroxy-4-methylpyrimidine-2-thione* (**10a**)

Method A: To a cooled ice bath a stirred solution of 1.990 g 4-isothiocyanatobutan-2-one (**8a**, 15.40 mmol) in 2 $cm^3$ MeCN was added 1.6 $cm^3$ 28 % aqueous solution of $NH_3$ (density of 0.895 g/$cm^3$), the reaction mixture was stirred at room temperature for 1.5 h, and the solvent was removed in vacuum. The residue was triturated with petroleum ether, and the precipitate was filtered and dried to give 1.755 g (78 %) **10a** as a white solid. M.p.: ~111 °C (decomp., acetone) (rate of heating was 1 °C/3 s; at lower rates of heating the compound decomposed without melting and then melted with decomposition at 147.5–148 °C) (Ref. [42] 127–128 °C, Ref. [45] 151–152 °C); $^1H$ NMR (DMSO-$d_6$): $\delta = 8.22$ (*br s*, 1H, $N_{(3)}H$), 8.13 (unresolved *d*, 1H, $N_{(1)}H$), 5.60 (*d*, $^4J_{OH,5\text{-}H} = 0.8$ Hz, 1H, OH), 3.18–3.29 (*m*, 1H, 6-Ha), 3.00–3.09 (*m*, 1H, 6-He), 1.66–1.75 (*m*, 1H, 5-He), 1.47–1.59 (*m*, 1H, 5-Ha), 1.35 (*s*, 3H, 4-$CH_3$) ppm; $^{13}C$ NMR (DMSO-$d_6$): $\delta = 175.33$ (C-2), 76.73 (C-4), 36.57 (C-6), 32.61 (C-5), 28.41 (4-$CH_3$) ppm; IR (Nujol): $\bar{\nu} = 3{,}357$ *s*, 3,219 *br vs* (ν NH, ν OH), 1,564 *s*, 1,530 *s* (thioamide-II), 1,204 *s*, 1,163 *s*, 1,123 *s*/cm.

Method B: To a cooled ice bath a stirred solution of 0.390 g 4-azidobutan-2-one (**5a**, 3.45 mmol) in 4 $cm^3$ dry THF and 2 $cm^3$ $CS_2$ was added 0.905 g $PPh_3$ (3.45 mmol). The resulting solution was stirred for 1.75 h at room temperature and refluxed for 1.5 h, and the solvent was removed in vacuum. The residue was triturated with diethyl ether–petroleum ether mixture (1:1 v/v) until crystallization was complete; the precipitate was filtered and washed several times with diethyl ether–petroleum ether mixture (1:1 v/v). The organic phases were combined, the solvent was removed in vacuum, and the oily residue, containing **8a** and small amount of $Ph_3PS$, was disolved in 4 $cm^3$ MeCN. Under stirring and cooling in an ice bath, to this solution was added 0.35 $cm^3$ 28 % aqueous solution of $NH_3$ (density of 0.895 g/$cm^3$). The obtained solution was stirred at room temperature for 1 h and the solvent was removed in vacuum. The residue was triturated with diethyl ether until crystallization was complete, the precipitate was filtered, washed with diethyl ether and dried to give 0.299 g (59 %) **10a** as a white solid.

Pyrimidine **10a** in DMSO-$d_6$ solution at room temperature slowly gave mixtures of **10a**, 1,2,3,4-tetrahydro-6-methylpyrimidine-2-thione (**12a**) and hexahydro-4-methylenepyrimidine-2-thione (**13a**). $^1H$ NMR spectrum of **12a** (DMSO-$d_6$): $\delta = 9.22$ (*br s*, 1H, $N_{(1)}H$), ~8.25 (*br s*, 1H, $N_{(3)}H$, signals overlap with the $N_{(3)}H$ signal of **10a**), 4.53–4.57 (*m*, 1H, 5-H), 3.72–3.75 (*m*, 2H, 4-H), 1.63–1.64 (m, 3H, 6-$CH_3$) ppm. $^1H$ NMR spectrum of **13a** (DMSO-$d_6$): $\delta = 10.02$ (*br s*, 1H, $N_{(3)}H$), 8.52 (*br s*, 1H, $N_{(1)}H$), 4.38 (unresolved *t*, 1H, = C–H), 3.94 (unresolved *t*, 1H, = C–H), 3.10–3.15 (*m*, 2H, 6-H), 2.37–2.41 (*m*, 2H, 5-H) ppm.

*Hexahydro-4-hydroxy-4,5-dimethylpyrimidine-2-thione* (**10b**)

Method A: To a cooled ice bath a stirred solution of 15.057 g **8b** (105.14 mmol) in 70 $cm^3$ MeCN was added dropwise 10 $cm^3$ 28 % aqueous solution of $NH_3$ (density of 0.895 g/$cm^3$), the reaction mixture was stirred for 10 min, then the ice bath was removed and stirring was continued at room temperature for 1 h. The solvent was removed in vacuum. The residue was triturated with diethyl ether, cooled, the precipitate was filtered, washed with cold diethyl ether and dried to give 15.010 g (89 %) **10b** as a mixture of (4*R**, 5*R**) and (4*R**, 5*S**)-diastereomers in a ratio of 94:6. After crystallization from acetonitrile, the diastereomeric ratio changed to 99:1. White solid, m.p.: 212–212.5 °C (decomp., MeCN) (Ref. [35] 187–188 °C); $^1H$ NMR of the major diastereomer (DMSO-$d_6$): $\delta = 8.22$ (*d*, $^4J_{N(3)H,\ N(1)H} = 2.0$ Hz, 1H, $N_{(3)}H$), 8.11 (unresolved *m*, 1H, $N_{(1)}H$), 5.47 (*d*, $^4J_{OH,\ 5\text{-}H} = 0.6$ Hz, 1H, OH), 2.85–2.96 (*m*, 2H, 6-Ha and 6-He), 1.55–1.68 (*m*, 1H, 5-H), 1.29 (*s*, 3H, 4-$CH_3$), 0.84 (*d*, $^3J_{CH_3 5-H} = 6.7$ Hz, 3H, 5-$CH_3$) ppm; $^1H$ NMR of the minor diastereomer (DMSO-$d_6$): $\delta = 8.06$ (*br s*, 1H, $N_{(1)}H$), 5.66 (*s*, 1H, OH), 3.40 (*ddd*, $^2J_{6\text{-}Ha,\ 6\text{-}He} = 12.5$, $^3J_{6\text{-}Ha,\ 5\text{-}H} = 4.4$, $^3J_{6\text{-}Ha,\ N(1)H} = 1.3$ Hz, 1H, 6-Ha), 2.74 (*ddd*, $^2J_{6\text{-}He,\ 6\text{-}Ha} = 12.5$, $^3J_{6\text{-}He,\ 5\text{-}H} = 3.8$, $^3J_{6\text{-}He,\ N(1)H} = 3.8$ Hz, 1H, 6-He), 1.68–1.78 (*m*, 1H, 5-H), 1.24 (*s*, 3H, 4-$CH_3$), 0.80 (d, $^3J_{CH_3,5-H}$= 7.0 Hz, 3H, 5-$CH_3$) ppm, the signal of the $N_{(3)}H$ proton overlaps with signal of the $N_{(1)}H$ proton of the major isomer; $^{13}C$ NMR of the major diastereomer (DMSO-$d_6$): $\delta = 175.16$ (C-2), 78.76 (C-4), 42.98 (C-6), 34.83 (C-5), 25.69 (4-$CH_3$), 11.80 (5-$CH_3$) ppm; $^{13}C$ NMR of the minor diastereomer (DMSO-$d_6$): $\delta = 174.81$ (C-2), 79.92 (C-4), 43.38 (C-6), 33.75 (C-5), 24.89 (4-$CH_3$), 13.91 (5-$CH_3$) ppm; IR (Nujol): $\bar{\nu} = 3{,}345$ *s*, 3,222 *br vs*, 3,138 *m* (ν NH, ν OH), 1,592 *s*, 1,532 *s* (thioamide-II), 1,213 *s*, 1,171 *s*, 1,036 *s*/cm.

Method B: Compound **10b** (3.388 g, 84 %) was prepared from 3.209 g 4-azido-3-methylbutan-2-one (**5b**, 25.24 mmol), 7.236 g $PPh_3$ (27.59 mmol), 15 $cm^3$ $CS_2$, 20 $cm^3$ dry THF, 16 $cm^3$ MeCN and 2.5 $cm^3$ 28 %

aqueous solution of $NH_3$ (density of 0.895 g/cm$^3$) as described for **10a** using method B.

Pyrimidine (4*R**, 5*R**)-**10b** in DMSO-$d_6$ solution at room temperature slowly gave mixtures of (4*R**, 5*R**)-**10b**, (4*R**, 5*S**)-**10b**, 1,2,3,4-tetrahydro-5,6-dimethylpyrimidine-2-thione (**12b**) and hexahydro-5-methyl-4-methylenepyrimidine-2-thione (**13b**). $^1$H NMR spectrum of **12b** (DMSO-$d_6$): $\delta$ = 9.06 (*br s*, 1H, $N_{(1)}H$), 8.16 (*br s*, 1H, $N_{(3)}H$), 3.61–3.63 (*m*, 2H, 4-H), 1.63–1.66 (*m*, 3H, 6-$CH_3$), 1.47–1.49 (*m*, 3H, 5-$CH_3$) ppm. $^1$H NMR spectrum of **13b** (DMSO-$d_6$): $\delta$ = 9.96 (*br s*, 1H, $N_{(3)}H$), 8.49 (*br s*, 1H, $N_{(1)}H$), 4.40–4.41 (*m*, 1H, = C–H), 3.99–4.01 (*m*, 1H, = C–H), 1.69–1.79 (*m*, 1H, 5-H), 1.04 (*d*, $^3J_{CH_3,5-H}$ = 6.7 Hz, 3H, 5-$CH_3$) ppm, signals of the 6-H protons overlap with proton signals of other compounds.

*Hexahydro-4-hydroxy-3,4-dimethylpyrimidine-2-thione* (**10c**)

To a cooled ice bath a stirred solution of 1.839 g **8a** (14.23 mmol) in 3 cm$^3$ MeCN was added 1.6 cm$^3$ 40 % aqueous solution of methylamine (density of 0.902 g/cm$^3$), the reaction mixture was stirred at room temperature for 1.5 h, and the solvent was removed in vacuum. The solid residue was triturated with petroleum ether; the precipitate was filtered and dried to give 1.869 g (82 %) **10c** as a white solid. M.p.: 91–91.5 °C (acetone) (Ref. [35] 85–86 °C); $^1$H NMR (DMSO-$d_6$): $\delta$ = 8.11 (unresolved *br t*, 1H, $N_{(1)}H$), 6.05 (*d*, 1H, $^4J_{OH,\ 5\text{-}H}$ = 0.3 Hz, OH), 3.17 (*s*, 3H, $NCH_3$), 2.97–3.19 (*m*, 2H, 6-Ha and 6-He), 1.82–1.96 (*m*, 2H, 5-Ha and 5-He), 1.38 (*s*, 3H, 4-$CH_3$) ppm; $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 177.56 (C-2), 81.74 (C-4), 36.23 (C-6), 35.32 (C-5), 33.17 (N–$CH_3$), 26.46 (4-$CH_3$) ppm; IR (Nujol): $\bar{\nu}$ = 3,346 *s*, 3,185 *br vs* (ν NH, ν OH), 1,534 *s*, 1,501 *s* (thioamide-II), 1,292 *s*, 1,156 *s*, 1,086 *s*/cm.

Pyrimidine **10c** in DMSO-$d_6$ solution at room temperature slowly gave equilibrium mixtures of **10c** and its acyclic isomer **11c**. $^1$H NMR spectrum of **11c** (DMSO-$d_6$): $\delta$ = 7.42 (very *br s*, 1H, $NHCH_3$), 7.37 (unresolved *br t*, 1H, $NHCH_2$), 3.50 (very *br s*, 2H, $CH_2N$), 2.78 (*br s*, 3H, N–$CH_3$), 2.69 (*t*, $^3J$ = 6.6 Hz, 2H, $CH_2C$=O), 2.09 (*s*, 3H, $CH_3C$=O) ppm; $^{13}$C NMR spectrum of **11c** (DMSO-$d_6$): $\delta$ = 207.58 (C=O), 182.40 *br* (C=S), 42.44 ($CH_2C$=O), 38.46 *br* ($CH_2N$), 30.60 *br* (N–$CH_3$), 29.95 ($CH_3C$=O) ppm.

*Hexahydro-4-hydroxy-3,4,5-trimethylpyrimidine-2-thione* (**10d**)

Compound **10d** (2.703 g, 73 %) was prepared from 2.705 g 4-azido-3-methylbutan-2-one (**5b**, 21.27 mmol), 6.091 g $PPh_3$ (23.22 mmol), 13 cm$^3$ $CS_2$, 20 cm$^3$ THF, 14 cm$^3$ MeCN and 2.3 cm$^3$ 40 % aqueous solution of methylamine (density of 0.902 g/cm$^3$) as described for **10a** using method B. This compound was obtained as a mixture of (4*R**, 5*R**)- and (4*R**, 5*S**)-diastereomers in a ratio of 99.5:0.5, respectively. After crystallization from acetonitrile the diastereomeric ratio did not change. White solid, m.p.: 116.5–117 °C (MeCN) (Ref. [35] 108–109 °C); $^1$H NMR of the major diastereomer (DMSO-$d_6$): $\delta$ = 8.02 (*dd*, $^3J_{NH,\ 6\text{-}He}$ = 4.1, $^3J_{NH,6\text{-}Ha}$ = 1.7 Hz, 1H, NH), 5.98 (*d*, $^4J_{OH,\ 5\text{-}H}$ = 0.4 Hz, 1H, OH), 3.16 (*s*, 3H, $NCH_3$), 3.11 (*ddd*, $^2J_{6\text{-}He,\ 6\text{-}Ha}$ = 12.8, $^3J_{6\text{-}He,\ 5\text{-}H}$ = 4.9, $^3J_{6\text{-}He,\ NH}$ = 4.1 Hz, 1H, 6-He), 2.77 (*ddd*, $^2J_{6\text{-}Ha,\ 6\text{-}He}$ = 12.8, $^3J_{6\text{-}Ha,\ 5\text{-}H}$ = 10.1, $^3J_{6\text{-}Ha,\ NH}$ = 1.7 Hz, 1H, 6-Ha), 1.96 (dddq, $^3J_{5\text{-}H,\ 6\text{-}Ha}$ = 10.1, $^3J_{5\text{-}H,\ J_{5-H,CH_3}}$ = 6.9, $^3J_{5\text{-}H,\ 6\text{-}He}$ = 4.9, $^4J_{5\text{-}H,\ OH}$ = 0.4 Hz, 1H, 5-H), 1.19 (*s*, 3H, 4-$CH_3$), 0.90 (*d*, $^3J_{CH_3,5-H}$ = 6.9 Hz, 3H, 5-$CH_3$) ppm; $^1$H NMR of the minor diastereomer (DMSO-$d_6$): $\delta$ = 8.14 (*br s*, 1H, NH), 5.85 (*s*, 1H, OH), 3.23 (*s*, 3H, $NCH_3$), 1.77–1.89 (*m*, 1H, 5-H), 1.38 (*s*, 3H, 4-$CH_3$), 0.91 (*d*, $^3J_{CH_3,5-H}$ = 6.7 Hz, 5-$CH_3$) ppm, signals of the 6-H protons overlap with protons signals of the major isomer and the acyclic form **11d** (see below); $^{13}$C NMR of the major diastereomer (DMSO-$d_6$): $\delta$ = 176.95 (C-2), 85.38 (C-4), 43.19 (C-6), 36.72 (C-5), 33.02 (N–$CH_3$), 20.55 (4-$CH_3$), 13.07 (5-$CH_3$) ppm; IR (Nujol): $\bar{\nu}$ = 3,438 *m*, 3,290 *vs*, 3,237 *vs* (ν NH, ν OH), 1,553 *s*, 1,509 *s* (thioamide-II), 1,289 *s*, 1,079 *s*/cm.

Pyrimidine **10d** (two diastereomers, 99.5:0.5) in DMSO-$d_6$ solution at room temperature slowly gave mixtures of (4*R**, 5*R**)-**10d**, (4*R**, 5*S**)-**10d**, and its acyclic isomer **11d**. $^1$H NMR spectrum of **11d** (DMSO-$d_6$): $\delta$ = ~7.41 (*br s* overlapped by the signals of the other NH group, 1H, $NHCH_3$), 7.41 (unresolved *br t*, 1H, $NHCH_2$), 3.53 (very *br s*, 1H, CH in $CH_2N$), 3.38 (very *br s*, 1H, CH in $CH_2N$), 2.79 (*br s*, 3H, N–$CH_3$), 2.13 (*s*, 3H, $CH_3C$=O), 0.99 (*d*, $^3J$ = 7.1 Hz, $CH_3CH$) ppm, signals of the CH proton in the $CHCH_3$ fragment overlap with proton signals of **10d**.

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