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Reactions of β-keto thioamides with α,β-unsaturated aldehydes. Synthesis of 6-hydroxypiperidine-2-thiones and 6*H*-thiopyrans

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Abstract—Mixtures of 3-benzoylated and 3-unsubstituted 6-hydroxypiperidine-2-thione derivatives were formed in the reaction of benzoyl(acetyl) thioacetamides with α,β-unsaturated aldehydes in refluxing ethanol in the presence of catalytic amounts of triethylamine. A mechanism for the debenzoylation was proposed. Derivatives of 6*H*-thiopyran were obtained when an analogous reaction was carried out in refluxing pyridine. The structures of all compounds were determined with the aid of 1D NMR (^{1}H, ^{13}C, ^{13}C-DEPT-135) and 2D NMR (^{1}H, ^{1}H COSY, ^{1}H, ^{1}H NOESY, ^{13}C, ^{1}H COSY) spectroscopy.

1. Introduction

A rapidly increasing recognition of the thioamide group as a useful moiety in organic synthesis has been brought out in the last decades. In fact, thioamides are known to readily react with both electrophilic and nucleophilic reagents to yield a wide variety of interesting compounds.[1] When treated with strong bases, they may be converted into anions and bis-anions.[1] Moreover, simple modifications of the fragments linked up with the thiocarbonyl group or with the thioamide nitrogen atom may give rise to the formation of new reactive centers and thus open up functionalization possibilities.

Several comprehensive reviews of the synthetic methods leading to the formation of thioamides and of the use of thioamides in organic synthesis have been published to date.[1–5] The most recent one is specifically concerned with the use of thioamides as universal and versatile building blocks in the synthesis of heterocyclic compounds.[1] Among numerous methods for thioamide functionalization those using regio-and stereoselective reactions of 1,4-type addition to α,β-unsaturated thioamides are particularly simple and useful.[6,7] Also thioamides can react according to the 1,4-addition mechanism with compounds having activated multiple bonds; this variant is similarly often used in the synthesis of heterocyclic compounds.[1] Nucleophilicity of the sulfur atom and/or the CH-acidic properties of the starting thioamide have to be considered as the driving forces of these reactions.

Bogdanowicz–Szwed and co-workers[8] reported the base-catalyzed reactions of β-keto acid thioacetanilides with arylmethylenemalonitriles and ethyl α-cyanocinnamates, which yielded 2-amino-6-thiooxopyridines. Similarly, in the reactions with β-nitrostyrenes, the indanone-derived thioamides gave the spirocyclic derivatives of tetrahydrothiophene.[9] A 1,4-addition of a β-keto thioamide anion to an unsaturated nitrile or nitrostyrene is involved in these reactions.

In our earlier papers we have described the bromine-dioxan-complex promoted reactions of intramolecular cyclization of *N*-allylthioamides derived from cyclic ketones and β-diketones as well as the reactions of β-keto thioamides with carboxylic esters.[10,11] Continuing our studies on the application of β-keto thioamides to the synthesis of heterocyclic compounds we report in this paper on the results of the reaction of secondary β-keto thioamides with α,β-unsaturated aldehydes.

2. Results and discussion

2.1. Reaction of β-keto thioamides with cinnamic and methylcrotonic aldehydes

α,β-Unsaturated aldehydes react with β-keto thioamides to afford the products of either the mixed aldol condensation or 1,4-addition. Every intermediate formed in that reaction may undergo a subsequent heterocyclization. Our investigations have supplied evidence that the structure of those heterocycles depended on both the structure of the thioamide and on the reaction conditions. Thus, benzoyl-thioacetamides **1a–c** react with cinnamaldehyde in refluxing ethanol in the presence of triethylamine to give a

Keywords: benzoyl thioacetamides; acetyl thioacetamides; 6-hydroxypiperidine-2-thiones; 6*H*-thiopyrans; 8,8-dimethyl-2-phenyl-3-thioxo-2-azabicyclo[2.2.2]octan-5-one.

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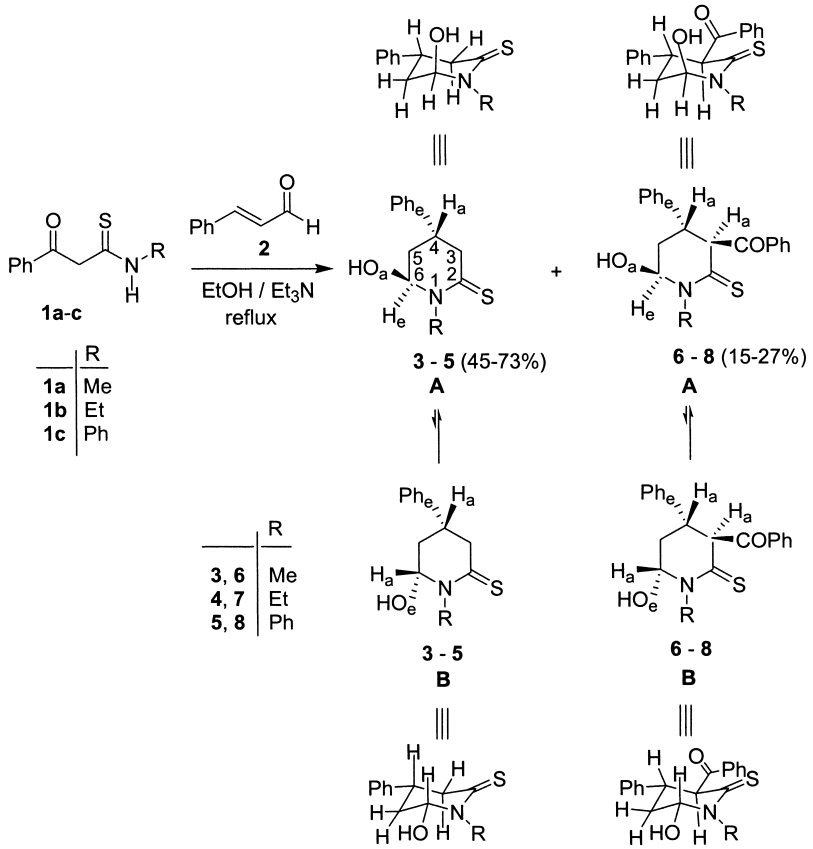
mixture of diastereoisomeric 6-hydroxypiperidine-2-thiones **3**-**5A**, **3**-**5B** and **6**-**8A**, **6**-**8B** (Scheme 1). A stereoselective 1,4-addition of nucleophile to aldehyde is the first step of this reaction. Subsequently, an intramolecular cyclization via the aldehyde group and the thioamide nitrogen gave rise to the formation of a mixture of C-6 epimers. A similar cyclization reaction, leading to the formation of diastereoisomers at the anomeric carbon, is well known in the carbohydrate chemistry.[12–15] It is interesting to note that the benzoyl group is lost from the cyclic products **6**-**8A**, **B** on prolonged heating to yield the debenzoylated analogs **3**-**5A**, **B** (Scheme 1). The reaction was carried on until the thioamide conversion was complete, and the **3**-to-**6** and **4**-to-**7**ratios were determined by GC/MS.

When the *N*-methyl- and *N*-ethylthioamides **1a** and **1b**, respectively, were heated with cinnamaldehyde for 12 h, diastereoisomeric mixtures of the benzoyl-containing (**6**, **7A**, **B**) and the debenzoylated (**3**, **4A**, **B**) compounds were formed in the 1:2 ratio (**6/3** and **7/4**). To make the debenzoylation complete, 20-h refluxing in ethanol was required. However, in the reaction of benzoylthioacetanilide **1c** with cinnamaldehyde, 11 h of refluxing was enough time to yield only the debenzoylated products (**5A**, **B**) as a mixture of diastereoisomers.

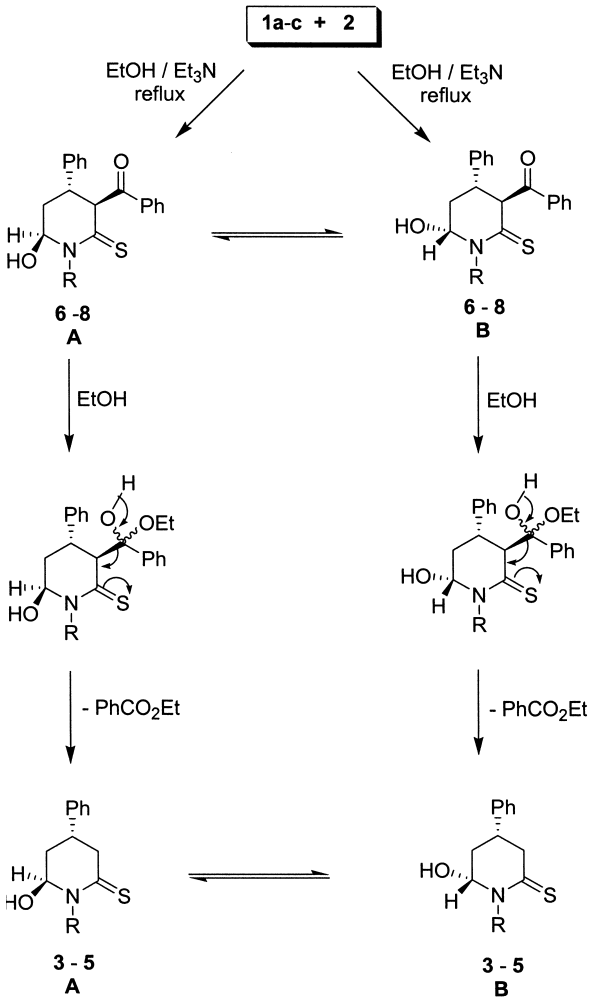
In order to investigate the solvent effects, in particular with regard to the debenzoylation process, the reactions of benzoyl *N*-ethylthioacetamide **1b** and benzoyl thioacetanilide **1c** with cinnamaldehyde were run in dry benzene and in trifluoroethanol; the latter was substituted for ethanol on account of its much lower basicity. With **1c**, debenzoylation was complete in both solvents and the only product isolated was a diastereoisomeric mixture **5A**, **B**, whereas with **1b** mixtures of benzoyl-containing (**7A**, **B**) and debenzoylated (**4A**, **B**) products were obtained. However, the **7/4** ratio was 2:1 in the reaction run in trifluoroethanol, and 1:1 in that run in benzene as calculated in the crude reaction products by means of GC/MS. Hydrolysis of the transient esters **7** and **8** in the benzene medium could be rationalized by assuming that traces of water were still present in the solvent in spite of routine drying (Scheme 3). Attempts at isolation of the esters were unsuccessful.

It is reasonable to assume, therefore, that the debenzoylation reaction follows a retro-Claisen-type condensation (Scheme 2). Nevertheless, an alternative mechanism involving transannular migration of the benzoyl group to the hydroxy oxygen and subsequent hydrolysis of the intermediate benzoic ester could not be ruled out at this stage (Scheme 3).

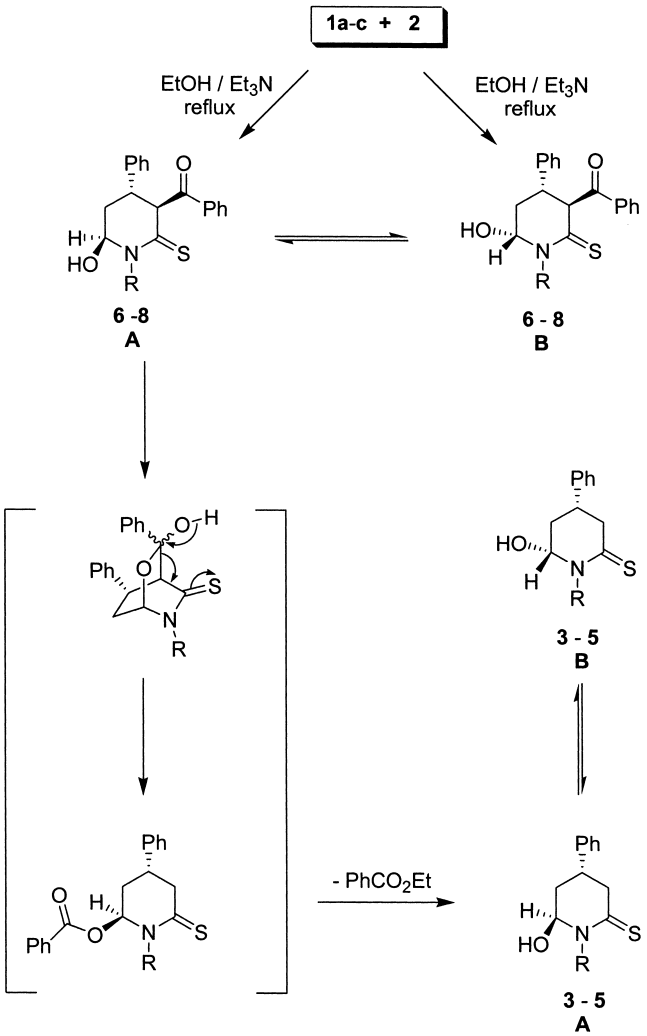
The reaction course was found to depend also on the structures of the thioamide and the unsaturated aldehyde. Thus, only the diastereoisomeric benzoyl-containing compounds **10**–**12A** and **10**–**12B** were formed in the reaction of thioamides **1a**–**c** with methylcrotonaldehyde **9** in refluxing ethanol containing triethylamine (Scheme 4). No debenzoylation was observed in these reactions.



Scheme 1.



Scheme 2.



Scheme 3.

When the benzoyl group was replaced in the starting thioamide with an acetyl group, the reactions unexpectedly took another course. Thus, the reaction of 3-oxo-*N*-phenylthiobutyramide **1d** with methylcrotonaldehyde **9** carried out in ethanol and in presence of triethylamine gave 8,8-dimethyl-2-phenyl-3-thioxo-2-azabicyclo[2.2.2]octan-5-one **14** (Scheme 5). In all probability, the primary reaction product **13** undergoes an intramolecular cyclization via the acetyl group.

Another factor affecting the reaction course is the solvent. When ethanol was replaced with pyridine, a Claisen-type condensation was the first step of the reaction. The intermediate diene thioamide **15** electrocyclized to give the thiopyran derivatives **16**–**19** (Scheme 6). There was no trace of the formation of products of the **16a**–**19a** type.

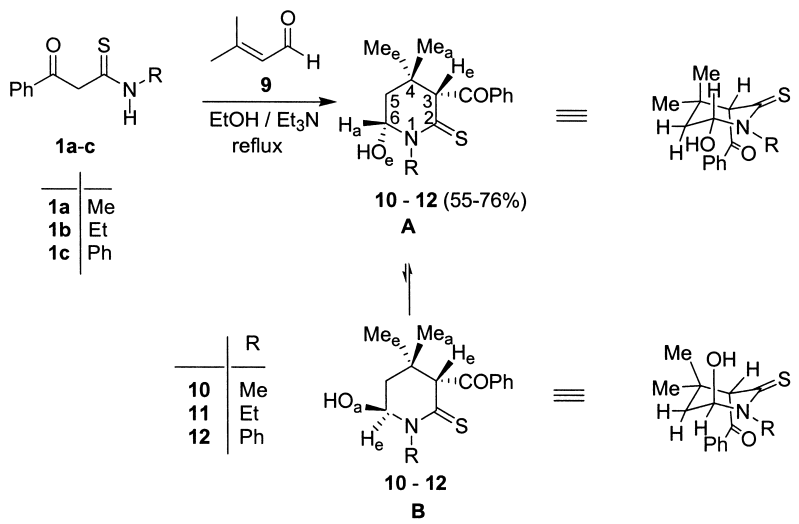
3. Structural assignments with the aid of NMR spectroscopy

The structures of all compound were elucidated with the aid of 1D NMR (^{1}H, ^{13}C, ^{13}C-DEPT-135) and 2D NMR (^{1}H, ^{1}H COSY, ^{1}H, ^{1}H NOESY, ^{13}C, ^{1}H COSY) spectroscopy.

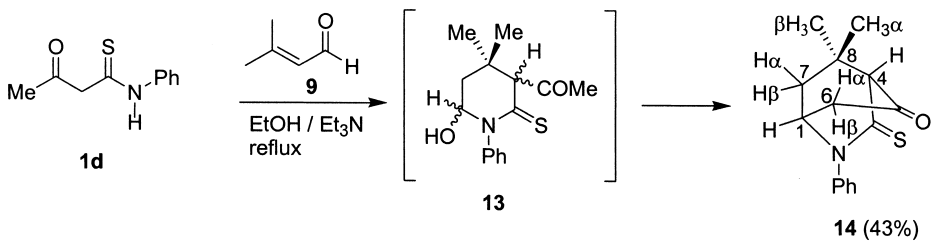
3.1. Structural analysis of compounds 6–7, 10–12

Analysis of the ^{1}H, ^{13}C, and ^{13}C DEPT-135 NMR spectra identifies compounds **3**–**7** and **10**–**12** as 6-hydroxy δ-thiolactams. This is evidenced by the chemical shift of C-6 appearing in the 80–84 ppm region and by the presence of an OH signal, the shape and chemical shift of which is concentration and solvent dependent. In a few cases, the analyses were more difficult owing to epimerization at C-6, which was observed in $CDCl_3$ or, more effectively, in a $CDCl_3$/DMSO 5:1 mixture (Table 1, Scheme 2 and 3). The ratios of epimers, as estimated by ^{1}H NMR spectroscopy, are presented in Table 1.

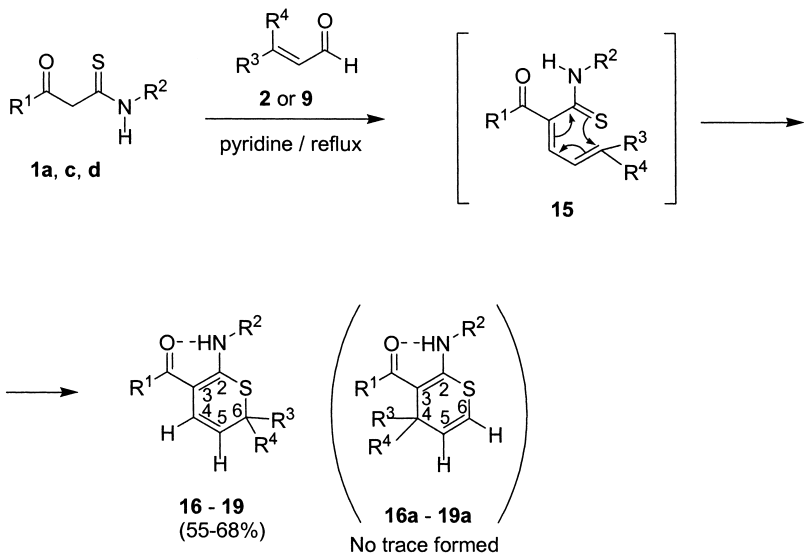
^{13}C NMR spectroscopy and the ^{13}C DEPT-135 method made it possible to easily identify both main products formed in the reaction of *N*-substituted 3-oxo-3-phenylthiopropionamide with cinnamaldehyde (Scheme 1). For instance, the C-3 signal appeared in the case of compound **4** at approximately 49.5 ppm, while in that of compound **7**, at 64.7 ppm. Both signals are in opposite phase as showed by DEPT-135 spectra. The configuration at C-6 of the major (**A**) and minor (**B**) epimers (compounds **3**–**7** and **10**–**12**), the configuration at C-3 (position of the benzoyl substituent in compounds **6**–**8**, **10**–**12**, and the configuration at C-4



Scheme 4.



Scheme 5.



	R^1	R^2	R^3	R^4
16	Me,	Ph,	Ph,	H
17	Ph,	Me,	Ph,	H
18	Ph,	Ph,	Ph,	H
19	Ph,	Ph,	Me,	Me

Scheme 6.

Table 1.

Compound	R	Solvent	Ratio of **A/B**
3	Me	$CDCl_3$	72:28
3	Me	$CDCl_3$/DMSO=5:1	73:27
4	Et	$CDCl_3$	89:11
5	Ph	$CDCl_3$	77:23
5	Ph	$CDCl_3$/DMSO=5:1	81:19
5	Ph	$CDCl_3$/DMSO=5:1 after 7 days	78:22
6	Me	$CDCl_3$	89:11
6	Me	$CDCl_3$ after 30 days	89:11
6	Me	$CDCl_3$/DMSO=5:1	87:13
6	Me	$CDCl_3$/DMSO=5:1 after 40 days	76:24
7	Et	$CDCl_3$	92:8
7	Et	$CDCl_3$/DMSO=5:1	80:20
8	Ph	Not isolated	–
10	Me	$CDCl_3$	98:2
11	Et	$CDCl_3$	100:0
12	Ph	$CDCl_3$	91:9
12	Ph	$CDCl_3$/DMSO=5:1	80:20

(position of the phenyl substituent in compounds **3**–**7**) were established by NMR analysis. This was based on the values of vicinal couplings found in the ^{1}H, ^{1}H COSY spectra and on the through-space interactions derived from the ^{1}H, ^{1}H NOESY experiment data. Since the routine ^{1}H NMR spectra did not allow for a direct determination of the coupling constants, the Lorentzian-to-Gaussian resolution enhancement was applied to obtain these data for the major (**A**) and, wherever possible, for the minor (**B**) epimers **3**–**7** and **10**–**12** (Table 2). The pseudo-equatorial and pseudo-axial hydrogen atoms in the assumed chair-like conformation of the piperidine-2-thione ring are referred to there as equatorial or axial, respectively.

Three spectral parameters were particularly helpful in determining the relative configuration at the C-3 and C-4 carbon atoms. Thus, high values (7.2–13.2 Hz) of the coupling constants between vicinal protons H-3 and H-4 in compounds **4**–**7** indicated their *trans*-diaxial orientation (Table 2); middling values (approximately 5 Hz) of the coupling constants between H-3 and H-4 in the 3-unsubstituted compounds **4** and **5** were characteristic of the H-3$_{eq}$H-4$_{ax}$ coupling type; low values of the coupling constants (W-shape type of $^4J_{HH}$) between equatorial protons H-3$_{eq}$ and H-5$_{eq}$ were observed in compounds **4**, **5** and **10**–**12**. Identification of the C-3- and C-4-attached protons made it possible to unambiguously assign H-5$_{eq}$, H-5$_{ax}$, H-6$_{ax}$, and H-6$_{eq}$ in the ^{1}H,^{1}H COSY spectrum and subsequently to assign the relative configuration at C-6 from the coupling constant data. These assignments were further confirmed from NOESY spectra. The diagnostic NOE interactions in the spectra of representative compounds **4**, **7**, and **10** are presented in Table 3 and in Figure 1.

It is noteworthy that relatively low values (6.0–9.3 Hz) of the vicinal coupling constants between H-5$_{ax}$ and H-6$_{ax}$ and high values (9.0–12.5 Hz) of the ^3J coupling constants between 6-OH$_{eq}$ and H-6$_{ax}$ protons were noted in both the major (**A**) epimers of **10**–**12** and the minor (**B**) epimers of **4**–**7**. In the epimers of opposite configuration, the 6–OH$_{eq}$–H–6$_{ax}$ coupling constants were significantly lower (approximately 6 Hz, Table 2).

3.2. Structural analysis of compound 14

Since in the case of **14** no acetyl CH_3 signal appears in its ^{13}C NMR and ^{13}C NMR 135 DEPT spectra and, moreover, there is no spectroscopic evidence for the presence of a C-6-attached hydroxy group, the structure of this compound must widely differ from that of **4**–**7** and **10**–**12**. A bicyclic structure was assigned to **14** with the aid of ^{1}H NMR spectroscopy which shows a low-field singlet (δ=3.81 ppm), a multiplet at δ=4.42 ppm and two similarly shaped sets characteristic of two methylene groups: one at 1.79 (dd) and 2.15 (dt) ppm, the other at 2.34 (dd) and 2.69 (dt) ppm. One of the two geminal coupling constants is evidently high (18.7 Hz) what indicates proximity of a carbonyl carbon atom.[16] The final proof of the bicyclic structure of **14** was supplied by a ^{1}H,^{1}H NOESY spectrum (Table 3, Fig. 1).

3.3. Structural investigations of the 6*H*-thiopyrane derivatives (16–19)

The structural analysis was based on the ^{1}H- and ^{13}C NMR, ^{13}C NMR, DEPT-135, and 2D NOESY spectra. Three essential informations were derived from the ^{1}H NMR spectra. First, the approximately 10-Hz coupling constant H-4–H-5 indicates an olefinic bonding with presumably *cis* configuration; second, coupling of H-4/H-5 with H-6 signifies allylic character of the H-6 proton; and last, the NH proton signal is shifted upfield owing to the presence of an intramolecular hydrogen bond which, as judged by the chemical shift of this signal, is stronger in **16**, **18**, and **19** (*N*–Ph) than in **17** (*N*–Me).

This structural identification called for additional evidence since the reactions of (β-keto thioamides with α,β-unsaturated aldehydes carried out in refluxing pyridine could have yielded the derivatives of 4*H*-thiopyrane **16a**–**19a** as well (Scheme 6). Cross-peaks observed in the 2D NOESY spectrum of **16** (R^1=CH_3, Scheme 6) provided the required proof. They indicate through-space interactions between: the acetyl group and H-4, H-4 and H-5, H-5 and H-6, as well as H-6 and the phenyl and hence strongly support the 6*H*-thiopyrane structural concept for **16**. The same structural conclusion may be derived from the ^{13}C NMR chemical shift data and signal phase in the ^{13}C NMR DEPT-135 spectra of **16**–**19**. All relevant spectral details are presented in Section 5.

4. Conclusions

Mixtures of 3-benzoylated and 3-unsubstituted 6-hydroxypiperidine-2-thione derivatives are formed in the reaction of benzoyl(acetyl) thioacetamides with α,β-unsaturated aldehydes in refluxing ethanol in the presence of catalytic amounts of triethylamine. Only the reaction of acetylthioacetanilide with methylcrotonaldehyde yields a bicyclic structure, 2-azabicyclo[2.2.2]octan-5-one. Both epimers of 6-hydroxypiperidine-2-thiones occur in solution. When pyridine is used instead of ethanol as the reaction medium, 6*H*-thiopyran derivatives are formed.

Table 2. Coupling constants obtained from Lorentzian to Gaussian resolution enhancement spectra

	3				**4**				**5**			
	$CDCl_3$/DMSO=5:1		$CDCl_3$		$CDCl_3$/DMSO=5:1		$CDCl_3$		$CDCl_3$/DMSO=5:1		$CDCl_3$	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
J_{HH} (Hz)[a]												
$J_{H\text{-}6ax OH\text{-}eq}$		8.6	–	6.1	–	8.3	–	5.5[b]	–	7.4	–	0
$J_{H\text{-}6eq OH\text{-}ax}$	6.2	–	[c]	–	6.4	–	6.9	–	6.5	–	0	–
$J_{H\text{-}5eq H\text{-}6eq}$	2.3	–	2.5	–	2.4	–	2.6	–	2.6	–	2.4	–
$J_{H\text{-}5eq H\text{-}6ax}$	–	5.6	–	6.1	–	6.0	–	7.5[b]	–	5.5	–	5.6
$J_{H\text{-}5ax H\text{-}6eq}$	4.1	–	3.8	–	3.6	–	3.6	–	2.6	–	3.6	–
$J_{H\text{-}5ax H\text{-}6ax}$	–	8.6	–	6.1	–	8.3	–	9.3[b]	–	7.5	–	7.7
$J_{H\text{-}5eq H\text{-}5ax}$	[d]	[d]	12.7	[d]	12.9	[d]	13.3	[d]	[d]	[d]	[d]	[d]
$J_{H\text{-}5eq H\text{-}3eq}$	2.3	[d]	2.5	[d]	2.4	[d]	2.5	[d]	1.9	[d]	2.0	[d]
$J_{H\text{-}5ax H\text{-}4ax}$	13.0	[d]	12.7	[d]	12.9	[d]	13.3	[d]	11.9	[d]	11.5	[d]
$J_{H\text{-}3eq H\text{-}3ax}$	[d]	[d]	18.2	16.7	18.2	[d]	18.6	[d]	18.6	[d]	18.6	[d]
$J_{H\text{-}3ax H\text{-}4ax}$	[d]	[d]	11.5	10.3	11.3	[d]	11.2	[d]	11.3	[d]	11.3	[d]
$J_{H\text{-}3eq H\text{-}4ax}$	[d]	[d]	~4.6	[d]	5.1	[d]	5.0	[d]	5.1	[d]	4.9	[d]

	6				**7**				**10**	
	$CDCl_3$/DMSO=5:1		$CDCl_3$		$CDCl_3$/DMSO=5:1		$CDCl_3$		$CDCl_3$	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
J_{HH} (Hz)[a]										
$J_{H\text{-}6ax OH\text{-}eq}$	–	8.6	–	[d]	–	8.0	–	[d]	0	–
$J_{H\text{-}6eq OH\text{-}ax}$	6.0	–	0		6.0	–	0	–	–	6.0
$J_{H\text{-}5eq H\text{-}6eq}$	2.9	–	3.0	–	2.9	–	2.9	–	–	1.8
$J_{H\text{-}5eq H\text{-}6ax}$	–	5.4	–	[d]	–	4.7	–	[d]	7.8	–
$J_{H\text{-}5ax H\text{-}6eq}$	2.9	–	3.2	–	3.5	–	2.9	–	–	6.0
$J_{H\text{-}5ax H\text{-}6ax}$	–	8.6	–	[d]	–	8.0	–	[d]	6.6	–
$J_{H\text{-}5eq H\text{-}5ax}$	13.3	13.3	[d]	[d]	13.4	13.7	13.3	[d]	14.6	14.3
$J_{H\text{-}5eq H\text{-}3eq}$	–	–	–	–	–	–	–	–	1.5	1.8
$J_{H\text{-}5ax H\text{-}4ax}$	13.3	[d]	13.8	[d]	13.4	[d]	13.3	[d]	–	–
$J_{H\text{-}3eq H\text{-}3ax}$	–	–	–	–	–	–	–	–	–	–
$J_{H\text{-}3ax H\text{-}4ax}$	10.6	10.8	7.2	7.2	10.7	11.0	6.8	6.8	–	–
$J_{H\text{-}3eq H\text{-}4ax}$	–	–	–	–	–	–	–	–	–	–

	11		**12**			
	$CDCl_3$/DMSO=5:1	$CDCl_3$	$CDCl_3$/DMSO=5:1		$CDCl_3$	
	A	**A**	**A**	**B**	**A**	**B**
J_{HH} (Hz)[a]						
$J_{H\text{-}6ax OH\text{-}eq}$	9.3	12.5	8.9	–	11.3	–
$J_{H\text{-}6eq OH\text{-}ax}$	–	–	–	6.3	–	6.0
$J_{H\text{-}5eq H\text{-}6eq}$	–	–	–	2.1	–	1.4
$J_{H\text{-}5eq H\text{-}6ax}$	6.2	8.0	6.2	–	8.0	–
$J_{H\text{-}5ax H\text{-}6eq}$	–	–	–	5.9	–	[d]
$J_{H\text{-}5ax H\text{-}6ax}$	9.3	6.0	8.8	–	6.2	–
$J_{H\text{-}5eq H\text{-}5ax}$	13.7	14.6	14.1	14.2	14.7	14.4
$J_{H\text{-}5eq H\text{-}3eq}$	2.2	1.9	2.0	1.8	1.6	1.5

[a] A=major epimer; B=minor epimer.
[b] Assignment could be interchanged.
[c] Broad signal.
[d] Coupling constant unreadable.

Configuration and conformation of the compounds prepared were determined with the aid of NMR spectroscopy. In the major epimers of the 3-benzoyl-substituted compounds **6A–7A** and **10A–12A**, the relationships of 6-hydroxy and 3-benzoyl groups are *cis*. In **6A–7A** hydroxy group occupied axial and benzoyl group equatorial positions, while in **10A–12A** the hydroxy group are in equatorial and benzoyl group are axial. The configurational distinction is presumably due to the change in the substitution at C-4. In **3A–7A**, the equatorial 4-phenyl and the axial 6-hydroxy groups are *trans* to one another.

5. Experimental

5.1. General

Melting points were determined with a digital Electrothermal apparatus, model IA9300, and are reported uncorrected. Infrared spectra were taken in KBr pellets with a Specord M80 instrument. ^1H, ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with an 5 mm ^1H/BB-inverse probe head, operating at 400.13 and 100.62 MHz with a digital

Table 3. Selected $^{1}H,^{1}H$ NOESY data for compound **4**, **7**, **10**, **14**

Compound	Perturbed signal	NOE answer[a]
4A		
	H-5_{ax}	H-5_{eq}(16.0); H-3_{ax}(4.2); OH(−2.1); H-6_{eq}(5.0); PhH(3.9)
	H-5_{eq}	H-5_{ax}(22.0); OH(−1.9); H-4_{ax}(5.4); H-6_{eq}(4.1); PhH(2.2)
	H-3_{ax}	H-5_{ax}(3.2); H-3_{eq}(22.5); PhH(3.2).
	H-6_{eq}	H-5_{ax}(4.0); H-5_{eq}(2.8);); C*H*H(3.7); OH(4.5); CH*H*(2.4)
7A		
	H-5_{ax}	H-5_{eq}(15.5); H-6_{eq}(1.5); PhH(4.0)
	H-5_{eq}	H-5_{ax}(20.2); H-4_{ax}(4.1); H-6_{eq}(2.0)
	H-4_{ax}	H-5_{eq}(2.6); PhH(3.7)
	H-6_{eq}	H-5_{ax}(2.3); H-5_{eq}(2.0); CH_3(2.4)
	H-3_{ax}	H-5_{ax}(1.1); PhH(3.4); PhHCO(8.0)
10		
	4-CH_{3eq}	4-CH_{3ax}(2.4), 5-CH_2(4.8), H-3_{eq}(2.0), PhHCO(2.2)
	4-CH_{3ax}	4-CH_{3eq}(2.6), 5-CH_2(2.3), H-6_{ax}(1.8), H-3_{eq}(2.5)
	N–CH_3	H-6_{ax}(2.3)
	6-OH_{eq}	5-CH_2(2.6), H-6_{ax}(−3.1)
	H-6_{ax}	6-OH_{eq}(−3.4), N–CH_3(3.5), 5-CH_2(5.6), 4-CH_{3ax}(1.7)
	H-3_{eq}	PhHCO(12.4), 4-CH_{3ax}(3.2), 4-CH_{3eq}(2.4)
14		
	H-4	$CH_3\alpha$(3.1); $CH_3\beta$(2.7)
	H-1	H-6β(2.7); H-6α(2.6); H-7β(2.8); H-7α(2.2)
	H-6β	H-6α(15.8)
	H-6α	H-7α(1.9); H-6β(16.6); $CH_3\alpha$(1.1)
	H-7β	H-7α(17.6), $CH_3\beta$(3.0)
	H-7α	$CH_3\alpha$(3.6)
	$CH_3\beta$	$CH_3\alpha$(2.7)

[a] Integrations of signals, calibrated relative to perturbed signals (value −100), are given in parentheses.

resolution of 0.12 and 0.97 Hz per point for ^{1}H and ^{13}C, respectively. TMS was used as internal reference in all measurements. Two-dimensional spectra were acquired using standard Bruker software. Heteronuclear correlation (^{13}C, ^{1}H COSY) was optimized for a coupling 145 Hz. In ^{1}H, ^{1}H NOESY experiments mixing times between 0.7 and 1.0 s were applied. Resolution enhanced spectra were obtained by Lorentzian-to-Gaussian transformation (LB=−2.5, GB=0.64) using standard Bruker software.

Purity and molecular mass determinations were carried out by gas chromatography-mass spectrometry (GC/MS) on a Hewlett–Packard instrument model HP 6890 equipped with a mass detector HP 5973. A 30 m long capillary column,

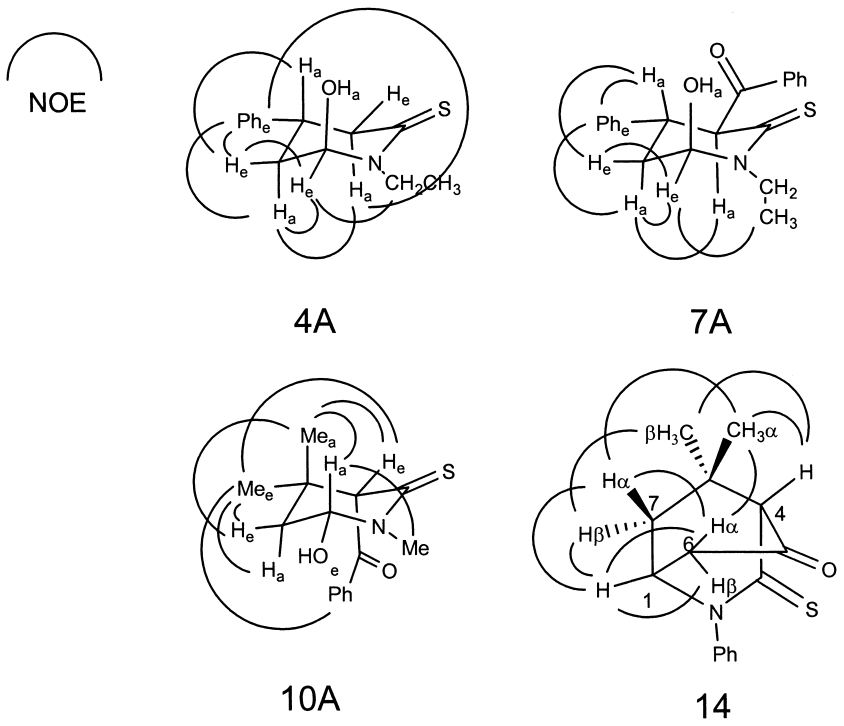


Figure 1. Diagnostic NOE interactions found in NOESY spectra.

0.2 mm in diameter, with methylsiloxane modified with phenyl groups (5% Ph, Me siloxane) in the 0.25 μm active phase layer was used for analytical purposes, and silica gel (0.04–0.063 mm, Merck) for preparative column chromatography. Elemental analyses were performed on EuroEA 3000 series, EuroVector CHNS-O Elemental Analyser. All compounds gave satisfactory elemental analysis (C, H, N, S).

β-Ketothioamides **1a–d** were synthesized according to known procedures.[17] Crude thioamides were purified by column chromatography with chloroform as the mobile phase. Final purification was done by recrystallization from toluene.

The thioamides, **1a**: mp 123–126°C (lit.[18] 123–124°C; lit.[19] 111–112°C); **1b**: mp 87–89°C (lit.[20] 75°C); **1c**: mp 78–80°C (lit.[21] 80–83°C; lit.[22] 74–77°C), **1d**: mp 59–62°C (lit.[23] 63–64°C; lit.[24] 61–62.5°C).

5.2. Synthesis of *N*-substituted 6-hydroxy-4-phenyl(4,4-dimethyl)piperidine-2-thiones (3–7, 10–12) and 8,8-dimethyl-2-phenyl-3-thioxo-2-azabicyclo[2.2.2]octan-5-one (14)

General procedure. A solution of β-keto thioamide **1a–d** (1 mmol), cinnamaldehyde **2** or methylcrotonaldehyde **9** (12 mmol), and triethylamine (25 mmol, 0.35 mL) in ethanol (50 mL) was refluxed until the thioamide substrate disappeared (12–14 h). The progress of the reaction was monitored by TLC (silufol/hexane-ethyl acetate 3:2). Upon evaporation of the solvent under reduced pressure, the crude products were chromatographed on silica gel using *n*-hexane/ethyl acetate (3:2) as the eluent. All solid compounds were purified by recrystallization from toluene.

5.2.1. (4*SR*,6*SR*)-6-Hydroxy-1-methyl-4-phenylpiperidine-2-thione (3A). Yield 45%. Yellow solid, mp 124–126°C; ν_{max} (KBr): 3332 (OH), 1518 (C=C) cm^{-1}; δ_H from the mixture of **3A/3B**=72:28 (**3A**; 400.1 MHz, $CDCl_3$) 2.18 (1H, td, J=13.5, 3.7 Hz, H-5_{ax}), 2.27 (1H, dq, J=13.6, 2.5 Hz, H-5_{eq}), 2.98 (1H, dd, J=18.2, 11.5 Hz, H-3_{ax}), 3.35–3.55 (2H, m, H-4_{ax}, H-3_{eq}), 3.52 (3H, s, N–CH_3), 3.83 (1H, br s, 6-OH_{ax}), 5.14 (1H, br s, H-6_{eq}), 7.14–7.35 (5H, m, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 32.77 (CH-4), 37.37 (CH_2-5), 41.45 (NCH_3), 49.16 (CH_2-3), 82.63 (CH-6), 126.60, 127.05, 128.04, 142.16 (C_6H_5), 200.58 (s, C=S). Anal. calcd for $C_{12}H_{15}NOS$: C 65.12, H 6.83, N 6.33, S 14.49. Found: C 65.69, H 6.92, N 6.07, S 14.13; *m/z*(EI, 70 eV): 203 (100, M^+-18), 170 (21), 144 (48), 115 (24), 91 (15), 42 (9).

5.2.2. (4*SR*,6*SR*)-1-Ethyl-6-hydroxy-4-phenylpiperidine-2-thione (4A). Yield 67%. Pale yellow solid, mp 106–108°C; ν_{max} (KBr): 3140 (OH), 1520 (C=C) cm^{-1}; δ_H from the mixture of **4A/4B**=89:11 (**4A**; 400.1 MHz, $CDCl_3$) 1.32 (5H, t, J=7.1 Hz, CH_3), 2.10 (1H, td, J=13.1, 3.6 Hz, H-5_{ax}), 2.28 (1H, dq, J=13.6, 2.5 Hz, H-5_{eq}), 2.92 (1H, dd, J=18.3, 11.2 Hz, H-3_{ax}), 3.30–3.53 (2H, m, H-4_{ax}, H-3_{eq}), 3.71 (1H, br s, 6-OH_{ax}), 3.79 (^{1}H, dq, J=13.3, 7.1 Hz, C*H*HCH$_3$), 4.46 (1H, dq, J=13.2, 7.1 Hz, CH*H*CH$_3$), 5.17 (1H, br s, H-6_{eq}), 7.18 (2H, d, J=7.2 Hz, C_6H_5), 7.20–7.28 (1H, m, C_6H_5), 7.32 (2H, t, J=7.1 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 11.65 (CH_3), 32.63 (CH-4), 37.58 (CH_2-5), 47.31 (*C*H_2CH$_3$), 49.51 (CH_2-3), 80.05 (CH-6), 126.62, 127.02. 128.82, 142.28 (C_6H_5), 199.69 (s, C=S). Anal. calcd for $C_{13}H_{17}NOS$: C 66.34, H 7.28, N 5.95, S 13.63. Found: C 66.92, H 7.27, N 5.90, S 13.63; *m/z*(EI, 70 eV): 217 (100; M^+-18), 184 (23), 158 (17), 131 (9), 115 (38), 91 (15).

5.2.3. (4*SR*,6*SR*)-6-Hydroxy-1,4-diphenylpiperidine-2-thione (5A). Yield 73%. Pale yellow solid, mp 183–185°C; ν_{max} (KBr): 3150 (OH), 1600 (C=C) cm^{-1}; δ_H from the mixture of **5A/5B**=81:19 (**5A**; 400.1 MHz, $CDCl_3$/DMSO=5:1) 2.24–2.26 (2H, m, H-5_{eq}, H-5_{ax}), 3.06 (1H, dd, J=18.5, 11.4 Hz, H-3_{ax}), 3.51–3.70 (2H, m, H-3_{eq}, H-4_{ax}), 5.26–5.31 (1H, m, H-6_{eq}), 6.58 (1H, d, J=6.5 Hz, 6-OH_{ax}), 7.24–7.39 (5H, m, 2C_6H_5), 7.47 (2H, t, J=7.6 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 32.67 (CH-4), 37.77 (CH_2-5), 49.72 (CH_2-3), 83.08 (CH-6), 126.62, 126.69, 127.59, 128.65, 128.68, 129.13, 143.11, 145.34 (2C_6H_5), 202.34 (s, C=S). Anal. calcd for $C_{17}H_{17}NOS$: C 72.05, H 6.05, N 4.94, S 11.32. Found: C 71.99, H 6.00, N 4.93, S 11.14; *m/z* (EI, 70 eV): 282 (72, M^+-1), 264 (100), 250 (91), 206 (50), 150 (66), 77 (95).

5.2.4. [(3*SR*,4*SR*,6*SR*)-(6-Hydroxy-1-methyl-4-phenyl-2-thioxopiperidin-3yl)](phenyl) methanone (6A). Yield 27%. Yellow solid, mp 196–198°C; ν_{max} (KBr): 3440 (OH), 1660 (C=O), 1590 (C=C) cm^{-1}; δ_H from the mixture of **6A/6B**=87:13 (**6A**; 400.1 MHz, $CDCl_3$/DMSO=5:1) 2.26 (1H, br d, J=ca. 10.4 Hz, H-5_{eq}), 2.39 (1H, td, J=13.4, 3.5 Hz, H-5_{ax}), 3.63 (3H, s, N–CH_3), 3.96 (1H, m, H-4_{ax}), 4.85 (1H, d, J=10.5 Hz, H-3_{ax}), 5.15 (1H, br s, H-6_{eq}), 6.79 (1H, d, J=6.0 Hz, OH_{ax}), 7.07–7.25 (5H, m, C_6H_5), 7.75 (2H, d, J=7.5 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 36.78 (CH_2-5), 37.72 (CH-4), 40.89 (NCH_3), 64.07 (CH-3), 81.91 (CH-6), 127.04, 127.20, 128.14, 128.59, 128.81, 132.42, 137.60, 140.77 (2C_6H_5), 196.93, 197.73 (C=O, C=S). Anal. calcd for $C_{19}H_{19}NO_2S$: C 70.12, H 5.88, N 4.30, S 9.85. Found: C 70.93, H 5.94, N 4.11, S 9.47; *m/z* (EI, 70 eV): 307 (3, M^+-18), 202 (100), 170 (13), 128 (4), 105 (23), 77 (16).

5.2.5. [(3*SR*,4*SR*,6*SR*)-(1-Ethyl-6-hydroxy-4-phenyl-2-thioxopiperidin-3-yl)](phenyl) methanone (7A). Yield 15%. Yellow solid, mp 154–156°C; ν_{max} (KBr): 3440 (OH), 1665 (C=O), 1600 (C=C) cm^{-1}; δ_H from the mixture of **7A/7B**=92:8 (**7A**; 400.1 MHz, $CDCl_3$) 1.38 (5H, t, J=7.1 Hz, CH_3), 2.23 (1H, td, J=13.3, 2.7 Hz, H-5_{ax}), 2.44 (1H, ddd, J=13.6, 4.9, 2.8 Hz, H-5_{eq}), 3.69–3.75 (1H, m, H-4_{ax}), 4.03 (1H, dq, J=13.1, 7.1 Hz, C*H*HCH$_3$), 4.35 (1H, dq, J=13.0, 7.1 Hz, CH*H*CH$_3$), 5.08 (1H, br s, 6-OH_{ax}), 5.22 (1H, br s, H-6_{eq}), 5.41 (1H, d, J=7.1 Hz, H-3_{ax}), 7.16–7.30 (5H, m, C_6H_5), 7.38 (2H, t, J=7.8 Hz, C_6H_5), 7.53 (1H, t, J=7.4 Hz, C_6H_5), 7.88 (2H, d, J=7.3 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 11.63 (CH_3), 38.07 (CH_2-5), 39.07 (CH-4), 48.61 (t, *C*H_2CH$_3$), 64.77 (CH-3), 80.77 (CH-6), 127.13, 127.43, 128.60, 129.04, 129.94, 133.91, 136.07, 142.13 (2C_6H_5), 194.88 (C=S), 200.88 (C=O). Anal. calcd for $C_{20}H_{21}NO_2S$: C 70.77, H 6.24, N 4.13, S 9.45. Found: C 71.13, H 6.25, N 4.13, S 9.56; *m/z* (EI, 70 eV): 321 (3, M^+-18), 216 (100), 184 (13), 155 (13), 105 (23), 77 (19).

5.2.6. [(3*RS*,6*RS*)-6-Hydroxy-1,4,4-trimethyl-2-thioxopiperidin-3-yl](phenyl)methanone (10A). Yield 70%. Yellow solid, mp 167–169°C; ν_{max} (KBr): 3500–3400 br (OH), 1750 (C=O), 1590 (C=C) cm^{-1}; δ_H from the mixture of **10A/10B**=98:2 (**10A**; 400.1 MHz, $CDCl_3$) 0.82 (5H, s, 4-CH_{3eq}), 1.13 (5H, s, 4-CH_{3ax}), 2.14 (1H, dd, J=14.6, 6.5 Hz, H-5_{ax}), 2.20 (1H, ddd, J=14.6, 7.9, 1.7 Hz, H-5_{eq}), 3.55 (5H, s, N–CH_3), 4.03 (1H, br s, 6-OH_{eq}), 4.99 (1H, br s, 6-H_{ax}), 5.23 (1H, d, J=1.5 Hz, H-3_{eq}), 7.51 (2H, t, J=7.9 Hz, C_6H_5), 7.62 (1H, t, J=6.7 Hz, C_6H_5), 8.12 (2H, d, J=7.2 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 27.97 (4-CH_3), 28.01 (4-CH_3), 34.89 (C-4), 40.05 (N–CH_3), 41.30 (CH_2-5), 67.25 (CH-3), 82.75 (CH-6), 128.89, 129.37, 133.92, 137.66 (C_6H_5), 195.31, 199.38 (C=O, C=S). Anal. calcd for $C_{15}H_{19}NO_2S$: C 64.95, H 6.90, N 5.05, S 11.56. Found: C 65.31, H 6.95, N 5.06, S 11.65; *m/z* (EI, 70 eV) (% I_{max}): 277 (32; M^+), 249 (33), 234 (45), 216 (11), 105 (100), 77 (36).

5.2.7. [(3*RS*,6*RS*)-1-Ethyl-6-hydroxy-4,4-dimethyl-2-thioxopiperidin-3-yl](phenyl)methanone (11A). Yield 76%. Pale yellow solid, mp 129–131°C; ν_{max} (KBr): 3420 (OH), 1660 (C=O), 1590 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81 (5H, s, 4-CH_{3eq}), 1.10 (5H, s, 4-CH_{3ax}), 1.33 (5H, t, J=7.1 Hz, CH_2CH_3), 2.12 (1H, dd, J=14.6, 6.1 Hz, H-5_{ax}), 2.20 (1H, ddd, J=14.6, 8.1, 1.8 Hz, H-5_{eq}), 4.00 (1H, dq, J=13.1, 7.1 Hz, CH*H*CH_3), 4.20 (1H, d, J=12.6 Hz, 6-OH_{eq}), 4.40 (1H, dq, J=13.1, 7.1 Hz, C*H*HCH_3), 5.03 (1H, ddd, J=12.6, 8.1, 6.1 Hz, 6-H_{ax}), 5.22 (1H, d, J=1.8 Hz, H-3_{eq}), 7.51 (2H, t, J=7.9 Hz, C_6H_5), 7.62 (1H, tt, J=7.4, 1.2 Hz, C_6H_5), 8.12 (2H, d, J=7.2 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 10.84 (CH_2CH_3), 27.92 (4-CH_3), 28.01 (4-CH_3), 35.13 (C-4), 41.40 (CH_2-5), 46.06 (NCH_2), 67.72 (CH-3), 80.65 (CH-6), 128.87, 129.37, 133.92, 137.72 (C_6H_5), 194.34, 199.44 (C=O, C=S). Anal. calcd for $C_{16}H_{21}NO_2S$: C 65.95, H 7.26, N 4.81, S 11.00. Found: C 65.65, H 7.28, N 4.77, S 11.01; *m/z* (EI, 70 eV): 291 (10, M^+), 273 (30), 230 (63), 168 (24), 105 (100), 77 (36).

5.2.8. [(3*RS*,6*RS*)-6-Hydroxy-4,4-dimethyl-1-phenyl-2-thioxopiperidin-3-yl](phenyl)-methanone (12A). Yield 55%. Yellow solid, mp 172–175°C; ν_{max} (KBr): 3460 (OH), 1660 (C=O), 1600 (C=C) cm^{-1}; δ_H from the mixture of **12A/12B**=91:9 (**12A**; 400.1 MHz, $CDCl_3$) 0.91 (5H, s, 4-CH_{3eq}), 1.34 (5H, s, 4-CH_{3ax}), 2.25 (1H, dd, J=14.7, 6.0 Hz, H-5_{ax}), 2.31 (1H, ddd, J=14.7, 8.0, 1.6 Hz, H-5_{eq}), 4.43 (1H, d, J=11.5 Hz, 6-OH_{eq}), 5.25 (1H, ddd, J=11.3, 7.7, 6.1 Hz, 6-H_{ax}), 5.37 (1H, d, J=1.5 Hz, H-3_{eq}), 7.28 (2H, br d, J=8.7 Hz, C_6H_5), 7.38 (1H, tt, J=7.4, 1.2 Hz, C_6H_5), 7.45–7.55 (5H, m, C_6H_5), 7.63 (1H, tt, J=7.4, 1.2 Hz, C_6H_5), 8.16 (2H, d, J=7.6, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 28.18 (4-CH_{3eq}), 28.43 (4-CH_{3ax}), 35.42 (C-4), 41.17 (CH_2-5), 67.92 (CH-3), 83.78 (CH-6), 127.63, 128.26, 128.94, 129.47, 129.60, 134.04, 137.72, 144.10 ($2C_6H_5$), 198.08, 199.35 (C=O, C=S). Anal. calcd for $C_{20}H_{21}NO_2S$: C 70.77, H 6.24, N 4.13, S 9.45. Found: C 70.86, H 6.23, N 4.08, S 9.12; *m/z* (EI, 70 eV): 321 (30, M^+-18), 306 (23), 278 (100), 200 (19), 105 (98), 77 (44).

5.2.9. 8,8-Dimethyl-2-phenyl-3-thioxo-2-azabicyclo-[2.2.2]octan-5-one (14). Yield 43%. Dark yellow solid, mp 172–174°C; ν_{max} (KBr): 2960 (CH_3), 2920 (–CH_2–), 1740 (C=O), 1590 (C=C) cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.14 (5H, s, 8-$CH_{3\alpha}$), 1.32 (5H, s, 8-$CH_{3\beta}$), 1.79 (1H, dd, J=13.6, 1.7 Hz, H-7_α), 2.15 (1H, dt, J=13.6, 3.7 Hz, H-7_β), 2.34 (1H, dd, J=18.7, 1.7 Hz, H-6_α), 2.69 (1H, dt, J=18.7, 3.3 Hz, H-6_β), 3.81 (1H, s, H-4), 4.40–4.44 (1H, m, H-1), 7.29–7.39 (5H, m, C_6H_5), 7.46 (2H, t, J=7.9 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 29.44 ($CH_{3\beta}$), 29.99 ($CH_{3\alpha}$), 34.56 (C-8), 40.27 (CH_2-7), 41.11 (CH_2-6), 60.94 (CH-4), 79.66 (CH-1), 125.46, 128.35, 129.66, 143.18 (C_6H_5), 195.87 (s, C=S), 203.83 (s, C=O). Anal. calcd for $C_{15}H_{17}NOS$: C 69.46, H 6.61, N 5.40, S 12.36. Found: C 69.69, H 6.60, N 5.39, S 12.33; *m/z* (EI, 70 eV): 258 (100, M^+-1), 202 (53), 189 (10), 174 (8), 120 (10), 77 (15).

5.3. Synthesis of 6*H*-thiopyrans (16–19)

General procedure. β-Keto thioamide **1a–d** (1 mmol) and cinnamaldehyde **2** or methylcrotonaldehyde **9** (12 mmol) were refluxed in pyridine (50 mL) for 11 h. After evaporation of the pyridine, the crude products were purified by column chromatography on silica gel with *n*-hexane/ethyl acetate (3:2) or chloroform to give the title compounds **16–19**. All solid compounds were further purified by recrystallization from toluene.

5.3.1. 1-(6-Phenyl-2-phenylamino-6*H*-thiopyran-3-yl)ethanone (16). Yield 55%. Dark oil; δ_H (400.1 MHz, $CDCl_3$) 2.35 (5H, s, CH_3), 4.80 (1H, dd, J=4.5, 1.6 Hz, H-6), 5.41 (1H, dd, J=10.0, 4.5 Hz, H-5), 6.71 (1H, dd, J=10.0, 1.7 Hz, H-4), 7.14–7.39 (15H, m, $2C_6H_5$), 14.07 (1H, s, NH); δ_C (100.6 MHz, $CDCl_3$) 27.65 (CH_3), 45.39 (C-6), 104.17 (C-3), 115.33 (C-5), 125.26, 126.29, 127.98, 128.17, 128.18, 128.75, 128.78, 137.99, 140.08 ($2C_6H_5$, C-4), 161.69 (C-2), 192.76 (C=O). Anal. calcd for $C_{19}H_{17}NOS$: C 74.23, H 5.57 N 4.56, S 10.43. Found: C 74.12, H 5.80, N 4.39, S 10.33; *m/z* (EI, 70 eV): 307 (100, M^+), 264 (51), 230 (37), 171 (7), 128 (12), 77 (19).

5.3.2. (2-Methylamino-6-phenyl-6*H*-thiopyran-3-yl)(phenyl)methanone (17). Yield 61%. Dark oil; δ_H (400.1 MHz, $CDCl_3$) 3.08 (5H, d, J=5.1 Hz, N–CH_3), 4.97 (1H, dd, J=4.7, 1.3 Hz, H-6), 5.15 (1H, dd, J=10.0, 4.8 Hz, H-5), 5.76 (1H, dd, J=10.0, 1.5 Hz, H-4), 7.28–7.53 (15H, m, $2C_6H_5$), 12.59 (1H, br s, NH); δ_C (100.6 MHz, $CDCl_3$) 31.47 (N–CH_3), 45.11 (C-6), 101.66 (C-3), 108.14 (C-5), 127.91, 128.02, 128.18, 128.89, 129.52, 140.75, 141.19 ($2C_6H_5$, C-4), 168.80 (C-2), 189.88 (C=O). Anal. calcd for $C_{19}H_{17}NOS$: C 74.23, H 5.57 N 4.56, S 10.43. Found: C 74.34, H 5.32, N 4.18, S 10.49; *m/z* (EI, 70 eV): 307 (100, M^+), 230 (96), 202 (33), 152 (33), 105 (43), 77 (45).

5.3.3. Phenyl-(6-phenyl-2-phenylamino-6*H*-thiopyran-3-yl)methanone (18). Yield 68%. Yellow solid, mp156–157°C; ν_{max} (KBr): 3500–3400 br (NH), 1620 (C=O), 1500 (C=C) cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 4.90 (1H, dd, J=4.4, 1.4 Hz, H-6), 5.31 (1H, dd, J=9.9, 4.5 Hz, H-5), 6.51 (1H, dd, J=9.9, 1.6 Hz, H-4), 7.20–7.36 (5H, m, $2C_6H_5$), 7.40–7.46 (5H, m, C_6H_5), 7.60–7.65 (2H, m, C_6H_5), 14.46 (1H, s, NH); δ_C (100.6 MHz, $CDCl_3$) 45.67 (C-6), 103.58 (C-3), 110.98 (C-5), 125.39, 126.59, 128.04, 128.27, 128.27, 128.43, 128.87, 129.07, 130.05, 138.25, 140.03, 140.82 ($3C_6H_5$), 130.23 (C-4), 165.16 (C-2), 190.94

(C═O). Anal. calcd for $C_{24}H_{19}NOS$: C 78.02, H 5.18 N 3.79, S 8.68. Found: C 78.06, H 5.20, N 3.70, S 8.7; *m/z* (EI, 70 eV): 367 (62, M^+-2), 338 (75), 262 (100), 187 (67), 115 (24), 77 (67).

5.3.4. (6,6-Dimethyl-2-phenylamino-6*H*-thiopyran-3-yl)(phenyl)methanone (19). Yield 59%. Yellow solid, mp 131–133°C; δ_H (400.1 MHz, $CDCl_3$) 1.48 (5H, s, $2CH_3$), 5.09 (1H, d, *J*=9.9 Hz, H-5), 6.27 (1H, d, *J*=9.9 Hz, H-4), 7.25–7.29 (5H, m, $2C_6H_5$), 7.30–7.35 (5H, m, C_6H_5), 7.55–7.58 (2H, m, C_6H_5), 14.27 (1H, s, NH); δ_C (100.6 MHz, $CDCl_3$) 29.36 ($2CH_3$), 44.78 (C-6), 103.08 (C-3), 119.23 (C-5), 125.33, 126.35, 127.43, 127.91, 128.34, 128.83, 138.45, 140.98 ($2C_6H_5$), 129.95 (C-4), 164.98 (C-2), 190.84 (C═O). Anal. calcd for $C_{20}H_{19}NOS$: C 74.73, H 5.96 N 4.36, S 9.98. Found: C 75.53, H 6.14, N 4.29, S 10.01; *m/z* (EI, 70 eV): 321 (100, M^+), 320 (22), 306 (176), 216 (24), 105 (88), 77 (79).

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