Tetrahedron 65 (2009) 1336–1348

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Michael addition of nitroalkanes to nonactivated α,β-unsaturated δ-thiolactams: reactivity, diastereoselectivity, and comparison to α,β-unsaturated δ-lactams

Jacek G. Sośnicki *

Szczecin University of Technology, Institute of Chemistry and Environmental Protection, Al. Piastów 42, PL-71065 Szczecin, Poland

ARTICLE INFO

Article history:
Received 12 October 2008
Received in revised form 18 November 2008
Accepted 11 December 2008
Available online 24 December 2008

Keywords:
Michael addition
Nitroalkanes
Reactivity
Diastereoselectivity
α,β-Unsaturated δ-(thio)lactams
5,6-Dihydro-1*H*-pyridine-2-(thi)one
4-Nitroalkylpiperidine-2-(thi)ones
FMO-theory

ABSTRACT

Aliphatic nitrocompounds add to nonactivated α,β-unsaturated δ-thiolactams leading to 4-nitroalkyl functionalized δ-thiolactams in good yields. The addition is a stereocontrolled process with respect to substituents at C-6, and takes place producing *trans* 4,6-disubstituted adducts in most cases. Ease of the addition has been studied in relation to the structure of the δ-thiolactam acceptors, within the FMO-theory. Comparative study with analogous δ-lactams has shown the advantages of α,β-unsaturated δ-thiolactams in Michael addition and indicated high prospects of these compounds in the synthesis of 4-functionalized piperidine derivatives.

1. Introduction

The Michael addition is one of the most important synthetic strategies available to the organic chemists.[1] Among the many applications, conjugate addition to α,β-unsaturated δ-lactams was used in the synthesis of functionalized piperidines, which, due to a wide range of biological activities,[2] are still an attractive synthetic goal.[3] Although the 1,4-addition of nucleophiles to nonactivated α,β-unsaturated lactams is difficult because of the electron-donating character of the nitrogen atom,[4,6] the addition of organometallic compounds is common.[5] Generally, the activation of α,β-unsaturated lactams toward conjugated addition by *N*-acyl,[6] *N*-tosyl,[7] *N*-*tert*-butoxycarbonyl[8] or C3-alkoxycarbonyl[9] groups has facilitated these reactions. However, the additions of metalloorganic heteronucleophiles have been reported[10] while the reactions with neutral heteronucleophiles have not.

Similar to α,β-unsaturated δ-lactams, α,β-unsaturated δ-thiolactams are promising Michael acceptors affording 4-substituted piperidine-2-thiones. They also form C–C bonds in the reaction with organometallics such as alkyllithium, alkylmagnesium,[11] and lithium enolates[12] and moreover, in contrast to nonactivated α,β-unsaturated δ-lactams, they easily react with neutral *N*- and *S*-nucleophiles.[13] Michael addition of neutral *N*-nucleophiles is not limited to α,β-unsaturated thiolactams because the products of the addition of amines to the open chain secondary and tertiary α,β-unsaturated thioamides were also successfully obtained.[14]

Among a broad range of nucleophiles applied to the C–C bond formation, the addition of aliphatic nitrocompounds play a significant role.[15] In the presence of a base catalyst, the introduction of a nitroalkyl group into a molecule allows a modification of the carbon skeleton and further transformation of the nitroalkyl group into many other functionalities.[16]

There are few fully described procedures in the literature, which provided adducts of α,β-unsaturated lactams with nitroalkanes. Amongst them procedures including lactams activated by *N*-*tert*-butoxycarbonyl (NBoc) group (Fig. 1, **1a**, **1b**,[17a] **1c**[17b]) and only one lactam without a typical electron-withdrawing group (Fig. 1, **1d**).[18] Recently, the addition of nitroalkanes to nonactivated *N*-(4-*F*-benzyl)-5,6-dihydropyridine-2-one (**1e**) was described, as one of the steps in the synthesis of naphthyridines, which exhibited an inhibition effect on HIV integrase.[19] However, no yields of the addition were given.

On the basis of our preliminary work, we have communicated that aliphatic nitrocompounds can be easily added to nonactivated α,β-unsaturated δ-thiolactams in the presence of DBU as catalyst,[20] yielding 4-nitroalkyl δ-thiolactams, which due to the high acidity of the hydrogen atoms at C-3 can be subsequently transformed to 3,4-disubstituted, subsequently to bicyclic (trans-fused) 2-piperidinones.[20b]

* Tel.: +48 91 4494798; fax: +48 91 4494639.
E-mail address: sosnicki@ps.pl

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.12.037

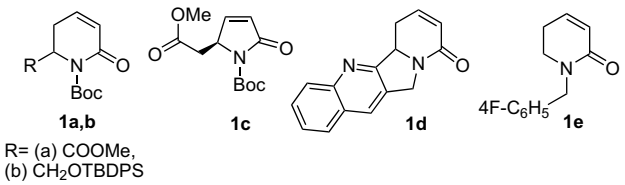


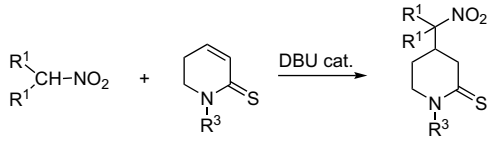
Figure 1. α,β-Unsaturated lactams successfully used as acceptors in Michael addition of nitroalkanes.

We have also demonstrated that 4-nitromethyl δ-thiolactams are valuable substrates in the synthesis of 4-isothiocyanato-2-piperidinones[21] and chiral pyrrolidin-2-ylidene carboxylate.[20a] However, no systematic study on Michael addition of nitrocompounds to α,β-unsaturated δ-thiolactams has been undertaken.

In continuation of our ongoing program aimed at the synthesis of 4-nitroalkyl δ-thiolactams and their application in the synthesis of polysubstituted piperidines, we now report an extended and detailed study on the Michael addition of nitroalkanes to α,β-unsaturated δ-thiolactams. The donors selected were nitromethane (**2a**), 2-nitropropane (**2b**), nitrocyclohexane (**2c**) and the thiolactam acceptors were NR (R=Me, Ph; **3a**, **3b**), 6-allyl NR (R=Me, Bn, Ph; **3c**–**e**), 6-(alkyl/aryl) NH (**3g**–**m**), and 6,*N*-diphenyl (**3f**) substituted 5,6-dihydro-1*H*-pyridine-2-thiones. The broad spectrum of the acceptors applied allowed identification of the factors influencing the reactivity, moreover, the application of 6-substituted α,β-unsaturated δ-thiolactams enabled examination of the diastereoselectivity of the addition. To compare the reactivity of α,β-unsaturated δ-thiolactams with that of the analogous α,β-unsaturated δ-lactams, a few runs of the additions of nitroalkanes to the latter were performed. An attempt was made to explain differences in the reactivity on the basis of the FMO-theory.

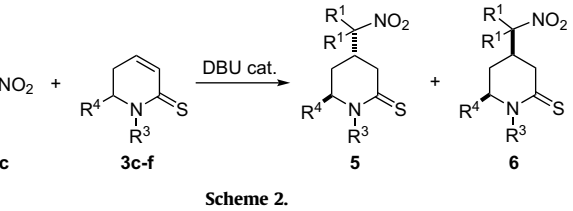
2. Result and discussion

The titled reactions have been divided into 3 groups, depending on the substitution pattern of α,β-unsaturated δ-thiolactam. The first group comprises NR substituted thiolactams **3a** and **3b** (Scheme 1), the second includes 6,*N*-disubstituted thiolactams **3c**–**f** (Scheme 2), while 6-substituted NH thiolactams **3g**–**m** belong to the third group (Scheme 3). The results and conditions of the above groups of reactions are presented in Tables 1–3, respectively.

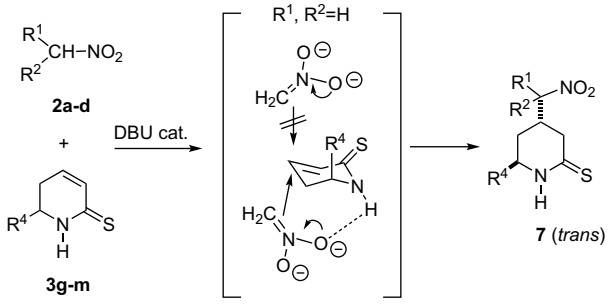


Scheme 1.

Generally, the Michael additions of nitroalkanes to α,β-unsaturated δ-thiolactams were carried out at room temperature and were catalyzed with 0.1–0.3 equiv of DBU. A greater amount of the catalyst accelerated the reaction but simultaneously diminished the yields (see, for example, Table 1, entries 2 and 3 or Table 3, entries 2 and 3). However, in a few cases, when a lower temperature (approx. −20 °C) was applied, 0.6 equiv of DBU was used. The optimum conditions of the addition included the excess of the nitrocompound, which also played the role of solvent (the excess of reagents **2a**, **2b** can be recovered on reaction completion). In the case of nitrocyclohexane, which cannot be easily removed, the reasonable minimum amount was used together with an additional small amount of CH_3CN. Reactions described in Table 2 (entries 10–13) as well as in Table 3 (entries 8 and 9) proved that the use of excess of **2** as neat solution was more effective. The progress of all reactions was monitored by TLC analysis at frequent time intervals dependent on total reaction time. The intermediate and final conversions of **3** and the ratio of diastereoisomeric products were estimated by ^{1}H NMR spectroscopy of the crude reaction mixtures.



Scheme 2.



Scheme 3.

Usually, the adducts were obtained in good yields and only regioselective 1,4-addition was observed. As far as the reactivity of acceptors is concerned, a significant influence of the type of *N*-substituent on the reactivity was observed. A comparison of the reactivities of thiolactams with the same substituents at position C-6 and a different one at the nitrogen atom showed that the NPh group made α,β-unsaturated δ-thiolactams more reactive, while the NMe substituted derivatives exhibited the lowest reactivity (see, for example, Table 1, entry 1 vs 2, 4 vs 6, 7 vs 8 or Table 2, entry 1 vs 2 vs 3). Taking into regard the final reaction times and the conversions of the substrates, the sequence of NR substituents accelerating the additions can be proposed as follows: NMe<NBn<NH<NPh. The substituent at C-6 also influenced the reactivity. Generally, the presence of a substituent at C-6 decreased the reactivity of α,β-unsaturated δ-thiolactams in relation to that of their 6-unsubstituted analogues, but in the case of the allyl substituent the reduction in activity was more pronounced than that of the derivatives with 6-phenyl group (see for comparison: Table 1, entry 6 vs Table 2, entries 8 and 9). This observation allows us to arrange the following sequence of C-6 substituents strengthening the reactivity of thiolactam acceptors: allyl<Ph<H. Both relations indicate that it is possible to control the reactivity of α,β-unsaturated δ-thiolactams by modifying the substituents at the nitrogen atom and at C-6.

With respect to diastereoselectivity, very interesting results were obtained. Secondary nitroalkanes **2b** and **2c** gave exclusively single *trans* 4,6-disubstituted products in all cases. Such a selectivity can be explained by the effect of steric interactions between the bulky donor and 6-substituent ($A^{1,3}$ strain).[22] The same complete diastereoselectivity was observed in the addition of secondary nitrocompounds to 6-substituted NBoc lactams **1a**, **1b**.[17a] In the same work, nitromethane as a small donor underwent addition with 1:1 or 1:3 cis/trans diastereoselectivity. In our investigation the formation of a cis/trans mixture was also observed for the addition of nitromethane (**2a**) to 6,*N*-disubstituted thiolactams **3c**–**f** (Table 2, entries 1–5). However, for 6-allyl acceptors the quantity of trans products **5c**–**e** grew in the sequence NMe<NBn<NPh (Table 2, entries 1, 2, and 3, respectively). Moreover, NPh derivative **3e** with

Table 1
Reaction conditions, yields of **4** obtained in the addition reactions of **2** with thiolactams **3a**, **3b** (according to Scheme 1)

Entry	**2a–c**	R^1	**3**	R^3	Equiv of **2** (equiv of CH_3CN)	Temp [°C]	Time [h]	Equiv of **DBU**	Conversion of **3**[a] [%]	**4**	Isolated yield **4** [%]
1	**2a** $MeNO_2$	H	**a**	Me	40 neat	rt	30	0.2	99	**a**	90
2			**b**	Ph	40 neat	rt	1	0.2	>99	**b**	91
3			**b**	Ph	40 neat	rt	0.5	0.6	99	**b**	50
4	**2b** *i*-$PrNO_2$	CH_3	**a**	Me	15 neat	rt	18	0.2	98	**c**	73
5			**a**	Me	40 neat	−20	2	0.6	97	**c**	86
6			**b**	Ph	15 neat	rt	0.5	0.2	>99	**d**	82
7	**2c** *c*-$HexNO_2$	$-(CH_2)_5-$	**a**	Me	1.5 (6.0)	rt	4	0.2	>99	**e**	96
8			**b**	Ph	1.5 (6.0)	rt	2	0.2	>98	**f**	72

[a] Estimated using ^{1}H NMR spectroscopy.

a 6-allyl substituent produced a more trans adduct (trans/cis=86:14; Table 2, entry 3) than NPh thiolactam **3f** with a larger 6-Ph substituent (trans/cis=67:33; Table 2, entry 4). A decrease in the temperature of the latter reaction did not change significantly the trans/cis product distribution (Table 2, entry 5). These results indicated that apart from steric effects, electronic effects also influenced the stereoselectivity of the addition. The latter is especially pronounced in the conjugation of the *N*-phenyl ring with the thioamide group: a large substituent at C-6 (Ph) disturbed the conjugation and changed the π-electron distribution in the PhNCS moiety. In this context, it could be assumed that the highest diastereoselectivity in the case of the 6-allyl and NPh substituted thiolactam is the effect of the best compromise between steric and electronic effects.

Interesting and surprising was the fact that 6-substituted NH thiolactams **3g–m** gave exclusively the trans product with nitromethane, irrespective of the size of the substituent at C-6, indicating NH as the group responsible for stereocontrolled addition. The high acidity of NH protons in secondary thioamides[23] and the synthetically proved interaction between chiral thioureas and nitrocompounds,[24] prompted us to assume that during the reaction course the hydrogen bond between the NH of the thiolactam and O_2NR (or their anionic form) is responsible for complete diastereoselectivity of the addition (Scheme 3).

To complete the above part of the study it should be noted that selective trans addition with respect to the 6-butyl group (in **3h**) was also noted to occur with nitroethane **2d** because trans 4,6-disubstituted product **7p** was obtained (Table 3, entry 20). However, because of the presence in **2d** of a stereogenic carbon atom as a neighbor to NO_2, a mixture of diastereomers was formed in this case. Besides, for practical reasons, β,γ-unsaturated thiolactams as easily obtainable and isomerizable upon treatment with DBU,[25] and the precursors of α,β-unsaturated δ-thiolactams **3a–e** can be directly used in the studied addition of nitroalkanes instead of **3a–e** without significant changes in the results.

For the sake of comparison, we examined the reactivity of α,β-unsaturated δ-lactams as analogues of the δ-thiolactams studied. Thus, a few runs of additions of nitroalkanes to the selected lactams were performed (Scheme 4, Table 4). The reactions were carried out applying α,β-unsaturated δ-lactams obtained by previous isomerization of β,γ-isomers with DBU in CH_3CN. After the equilibrium states of the mixtures of β,γ-(**1(a)**) and α,β-unsaturated (**1(b)**) δ-lactams were reached in 4 days (Table 4, Scheme 4, Path A), the solvent was removed and to the residue appropriate nitroalkanes were added (Scheme 4, Path B). The results supported low reactivity of lactams relative to that of their activated derivatives (Fig. 1) or their thio analogues (Schemes 1–3). Two of the four reactions performed gave no positive result at all. The addition of

Table 2
Reaction conditions, yields, and ratio of **5**:**6** obtained in the addition reactions of **2** with thiolactams **3c–f** (according to Scheme 2)

Entry	**2**	R^1	**3**	R^3	R^4	Equiv of **2** (equiv of CH_3CN)	Temp [°C]	Time	Equiv of **DBU**	Conversion. of **3** [%]; (ratio of **3**:**5**+**6**)[a]	**5**:**6** (R^1)	**5**:**6** Ratio[a]	Isolated yield **5**, **6** [%]
1	**2a** $MeNO_2$	H	**c**	Me	Allyl	180 neat	rt	3 d	0.2	(50:50)	**a**	~50:50	
								6 d		(35:65)		~50:50	
								10 d		(28:72)		~50:50	
								16 d		(21:79)		~50:50	
								18 d		80 (21:79)		~50:50	57
2			**d**	Bn	Allyl	180 neat	rt	1 d	0.2	(18:82)	**b**	~60:40	
								2 d		(4:96)		~60:40	
								3 d		99 (0:100)		~60:40	95
3			**e**	Ph	Allyl	180 neat	rt	24 h	0.2	99	**c**	86:14	72
4			**f**	Ph	Ph	180 neat	rt	18 h	0.2	>99	**d**	67:33	79
5			**f**	Ph	Ph	60 neat	−20	29 h	0.6	96	**d**	68:32	80
6	**2b** *i*-$PrNO_2$	CH_3	**c**	Me	Allyl	10 neat	rt	20 h	0.3	90	**e**	>99:1	69
7			**d**	Bn	Allyl	10 neat	rt	3 h	0.3	>99	**f**	>99:1	90
8			**e**	Ph	Allyl	10 neat	rt	2.5 h	0.3	>99	**g**	>99:1	88
9			**f**	Ph	Ph	20 neat	rt	1 h	0.3	>99	**h**	>99:1	75
10	**2c** *c*-$HexNO_2$	$-(CH_2)_5-$	**c**	Me	Allyl	1.5 (6.0)	rt	42 h	0.2	(1:0.34)			
								7 d		(1:0.37)			
								12 d		20 (1:0.37)	**i**	>99:1	ca. 9
11			**c**	Me	Allyl	4.0 neat	rt	4 d	0.2	(1:1.3)			
								8 d		49 (1:1.3)	**i**	>99:1	38
12			**d**	Bn	Allyl	1.5 (6.0)	rt	7 d	0.2	57	**j**	>99:1	39
13			**d**	Bn	Allyl	4.0 neat	rt	3 d	0.2	97	**j**	>99:1	62
14			**e**	Ph	Allyl	1.5 (6.0)	rt	30 h	0.2	97	**k**	>99:1	65
15			**f**	Ph	Ph	1.5 (6.0)	rt	2.5 h	0.2	98	**l**	>99:1	63

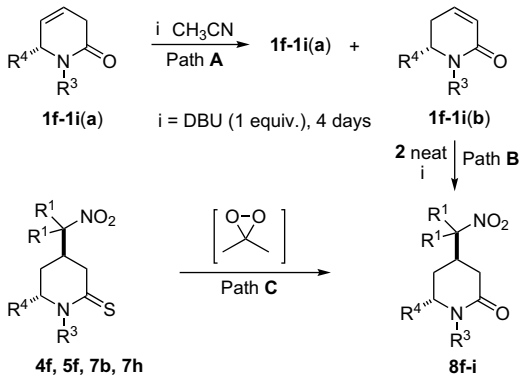
[a] Estimated using ^{1}H NMR spectroscopy.

Table 3
Reaction conditions, yields of **7** obtained in the addition reactions of **2** with thiolactams **3k–m** (according to Scheme 3)

Entry	**2a–d**	R^1, R^2	**3**	R^4	Equiv of **2** (equiv of CH_3CN)	Temp [°C]	Time [h]	Equiv of **DBU**	Conversion of **3**[a]	**7**	Isolated yield **7** [%]
1	**2a** $MeNO_2$	H, H	**g**	Et	26 neat	rt	4.5	0.2	>99	**a**	80
2			**h**	*n*-Bu	30 neat	rt	3	0.2	99	**b**	88
3			**h**	*n*-Bu	60 neat	rt	1	0.5	99	**b**	80
4			**i**	*n*-Hex	25 neat	rt	5	0.2	>99	**c**	79
5			**j**	*t*-Bu	30 neat	rt	24	0.2	>99	**d**	78
6			**k**	Ph	30 neat	rt	48	0.2	94	**e**	40
7			**l**	Allyl	25 neat	rt	2.5	0.3	>99	**f**	64
8	**2b** *i*-$PrNO_2$	CH_3, CH_3	**g**	Et	10 neat	rt	1.5	0.1	>99	**g**	90
9			**g**	Et	3 (10)	rt	2.0	0.1	>99	**g**	80
10			**h**	*n*-Bu	10 neat	rt	5	0.1	>99	**h**	88
11			**h**	*n*-Bu	3 (10)	−20	20	0.6	98	**h**	77
12			**i**	*n*-Hex	10 neat	rt	1.5	0.1	>99	**i**	73
13			**j**	*t*-Bu	9 neat	rt	1.5	0.3	>99	**j**	86
14			**k**	Ph	10 neat	rt	1	0.2	95	**k**	44
15			**m**	*sec*-Bu	10 neat	rt	1	0.3	>99	**l**	72 (50:50)[b]
16	**2c** *c*-$HexNO_2$	$-(CH_2)_5-$	**g**	Et	1.5 (10)	rt	2.5	0.1	>99	**m**	76
17			**h**	*n*-Bu	1.6 (6)	rt	3	0.1	96	**n**	76
18			**h**	*n*-Bu	2 (6)	−22	17	0.6	>99	**n**	83
19			**i**	*n*-Hex	1.5 (10)	rt	4	0.1	>99	**o**	80
20	**2d** $EtNO_2$	H, CH_3	**h**	*n*-Bu	60 neat	rt	4.5	0.2	>99	**p**	86 (53:47)[b]

[a] Estimated using ^{1}H NMR spectroscopy.
[b] Mixture of diastereomers.

nitromethane to NH lactam **1f(b)** gave selectively the trans adduct **8f** (probably via the same NH···O_2N hydrogen bond assistance as for thiolactams **3g–m**) in 17% yield together with 60% conversion of the unsaturated δ-lactam **1f(a)**. The best result was obtained for NPh lactam **1i**, which produced adduct **8i** in 37% yield (50% conversion of the substrate).



Scheme 4.

Finally, ending the synthetic part of this study, we want to show that the above ineffective, direct synthesis of 4-nitroalkyl δ-lactams from α,β-unsaturated δ-lactams can be replaced with a two-step sequential synthesis including an effective addition of nitrocompounds to α,β-unsaturated δ-thiolactams and subsequent S to O transformation of 4-nitrothiolactams, e.g., by the treatment with dimethyl dioxirane[26] generated in situ (Scheme 4). To illustrate the above synthetic possibilities 4-nitroalkyl δ-thiolactams **4f**, **5f**, **7b**, **7h** were converted into the corresponding δ-lactams in good yields (Scheme 4, Path C; Table 4).

An attempt at rationalization of the experimentally observed relations between the structures of δ-(thio)lactams and their reactivity toward addition was made in terms of the frontier molecular orbital (FMO) theory. Because the LUMO energy of the acceptor determines its reactivity in the Michael addition, which is the greater with a decrease in energy,[1a] the LUMO energies of compounds **3** and **1** were calculated. The semiempirical method PM3[27] was selected for calculation because this method didn't require time-consuming calculations and gave reasonable results in the explanation of the reactivity of linear α,β-unsaturated thioamides.[14] The calculated energies of LUMOs of the sets of compounds are presented in graphical form in Figure 2. In order to complete the above data, the LUMO energies of the compounds not synthesized in this study were also calculated. For 6-substituted derivatives the average values of LUMO energy for *quasi* 6-axial and 6-equatorial structures were given.

The main conclusion from the above presented results is that the LUMO energies change in parallel to the experimentally observed reactivity of the acceptors. Generally, the LUMO energies of thiolactams are much lower than those of lactams, which makes the former much more reactive. In both sets of compounds some further structural dependence on the LUMO level parallel to experimental results should be pointed out. The most striking is that

Table 4
Synthesis of 4-nitroalkylpiperidin-2-ones **8** (according to Scheme 4)

Entry	**1(a)**	R^1	R^3	R^4	Ratio of **1(b):1(a)** (Path **A**)	Equiv (**2**)	**8**	Yield **8**[a] [%] (Path **B**)	Conv. of **1(a)**+**1(b)** (Paths **A** and **B**) [%]	Yield **8** [%] (Path **C**)	Substrates used (Path **C**)
1	**1f(a)**	H	H	Bu	7:3	40 (**2a**)	**f**	17	60	93[b] (82)[c]	**7b**
2	**1g(a)**	Me	H	Bu	7:3	20 (**2b**)	**g**	Traces	~0	96[b] (84)[c]	**7h**
3	**1h(a)**	Me	Bn	Allyl	8:2	20 (**2b**)	**h**	Traces	~0	93[b] (83)[c]	**5f**
4	**1i(a)**	$-(CH_2)_5-$	Ph	H	9:1	3 (**2c**)	**i**	37	50	87[b] (63)[d]	**4f**

[a] Yield assigned by ^{1}H NMR spectroscopy and calculated with respect to **1f–1i(a)**.
[b] Isolated yields.
[c] Overall yields calculated with respect to β,γ-unsaturated isomers of **3**.
[d] Overall yield calculated with respect to **3**.

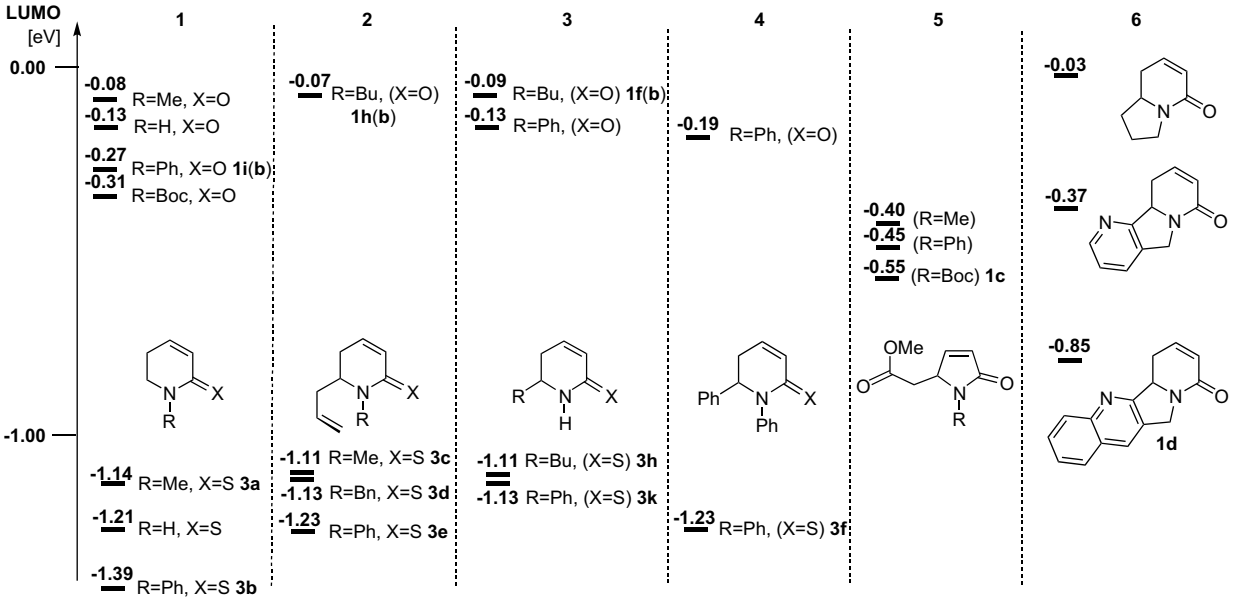


Figure 2. PM3 calculated energies of LUMO orbitals of α,β-unsaturated δ-thiolactams and lactams.

the presence of a phenyl ring at nitrogen decreases the energy of LUMO relative to that of NH (Δ=0.14–0.18 eV) and by even more relative to that of NMe derivatives (Δ=0.19–0.25 eV) because of the phenyl group conjugation. The substituent at C-6 increases the LUMO energy of acceptors in comparison to that of 6-unsubstituted ones, which makes the 6-substituted derivatives less reactive. The energies of LUMOs of NBoc lactams varied from −0.31 eV to −0.55 eV (**1c**) are lower than that of NH and NR derivatives. Differences in the LUMO energies of both lactams explain the activation role of NBoc group in Michael addition (Fig. 2). FMO's theory approach allowed also better understanding of the addition of nitroalkane to lactam **1d**,[18] which is not activated by standard groups. Thus, good reactivity of lactam **1d** is reflected by low energy of LUMO (−0.85 eV, Fig. 2, Column 6).

In order to identify the element of lactam **1d** responsible for the low LUMO energy, the calculations were performed for the two hypothetical structures obtained as a result of removal of the benzene and pyridine rings from the parent compound **1d**. The LUMO energy values obtained for these hypothetical structures increased with decreasing contribution of the aromatic rings. This result implies that the presence of the chinoline ring in lactam **1d** determines the low LUMO energy and is responsible for its increased reactivity.

The structures of all compounds were elucidated with the aid of 1D NMR (^{1}H,^{13}C, ^{13}C-DEPT-135) and 2D NMR (^{1}H,^{1}H COSY, ^{13}C,^{1}H COSY spectroscopy). The configurations at C-4 and C-6 were established by tentative conformational analysis assuming the chair-like conformation of the piperidine-2-thione ring, where hydrogen atoms were denoted as equatorial or axial. The configurational and conformational analyses were based on the values of *J*-coupling constants found in ^{1}H NMR and the relation between *J* and H,H dihedral angles[28] and cross couplings peaks found in ^{1}H,^{1}H COSY spectra. The obtained structures were supported with the through-space distances derived from the ^{1}H,^{1}H NOESY for compounds **5d**, **5e**, and **7k**. Since the routine ^{1}H NMR spectra did not allow direct determination of the coupling constants in some cases, the resolution enhancement by digitalized filtering was applied to obtain these data.

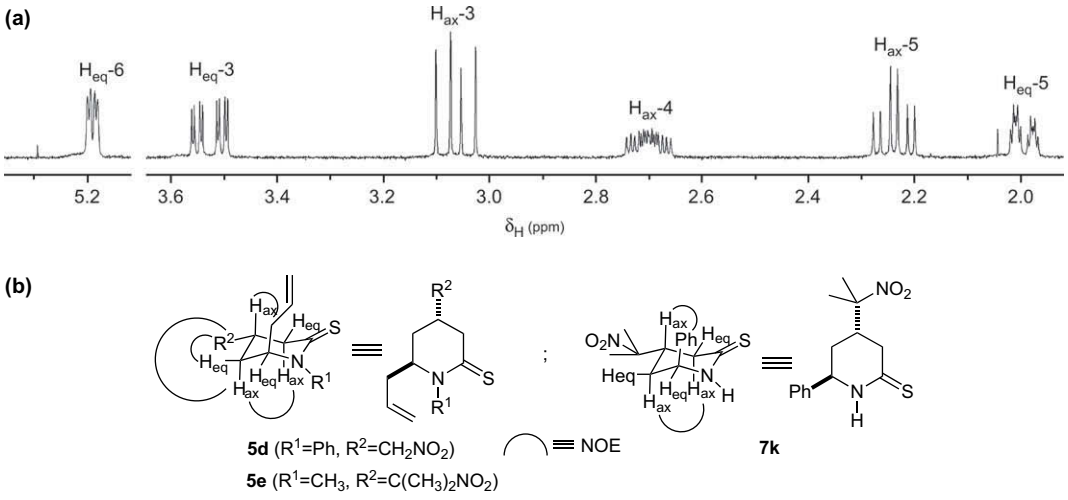


Figure 3. (a) Fragmental ^{1}H NMR spectra of **5h**. (b) Diagnostic NOE effects found in ^{1}H,^{1}H NOESY of **5d**, **5e**, and **7k**.

Based on the above analysis, all main products of 4,6-disubstituted piperidine-2-thiones were established as trans isomers, where 4- and 6-substituents are equatorially and axially oriented, respectively. The ^{1}H NMR spectrum of **5h** with nonoverlapped multiplets best illustrates the analysis performed (Fig. 3, upper). In the ^{1}H NMR spectrum of **5h** one of two geminal protons at C-3 gives a characteristic doublet of doublets (dd) at 3.05 ppm with two large coupling constants ($J_{Hax\text{-}3\text{–}Heq\text{-}3}$=18.9 Hz and $J_{Hax\text{-}4\text{–}Hax\text{-}3}$=11.1 Hz), indicating its axial position (CH_{ax}-3). The second hydrogen atom at C-3 appears as doublet of multiplets (dm) with one large geminal and a few small coupling constants and is concluded as CH_{eq}-3. These two multiplets and dddd at 2.7 ppm (*J* 12.9, 11.1, 6.2, 3.2 Hz), which is of CH_{ax}-4 origin indicated the equatorial position of 4-nitroalkyl group. It should be noted that the nitromethyl group at C-4 adopts an equatorial position in all 4-monosubstituted compounds. The triplet of doublets at 2.22 ppm ($J_{Hax\text{-}5\text{-}Hax\text{-}4}$=12.9, $J_{Hax\text{-}5\text{-}Heq\text{-}5}$=12.9, $J_{Hax\text{-}5\text{-}Heq\text{-}6}$=5.4 Hz) assigned to CH_{ax}-5 and the doublet of doublets at 5.2 ppm (dd, *J* 5.4, 2.2 Hz) assigned to CH-6$_{eq}$ supported the axial position of the substituent at C-6. The above pattern of splitting appears in the ^{1}H NMR spectra of all trans isomers with small deviations in the case of 4-nitromethyl derivatives, even when some signals are overlapped. The cross couplings found in NOESY spectra of **5c**, **5d**, and **7k** supported the proposed configuration and conformation of 4,6-disubstituted derivatives (Fig. 3).

For the sake of comparison, the isolated *cis* 4,6-disubstituted isomer **6d** exhibited the same coupling constants pattern for CH_{eq}-3 (CH_{ax}-3 is overlapped) as for the trans isomers, indicating the equatorial position of the 4-nitromethyl group. However, the CH_{ax}-5 proton, which gave a doublet of triplets (dt) with three large coupling constants ($J_{Hax\text{-}5\text{–}Hax\text{-}4}$=13.9, $J_{Hax\text{-}5\text{–}Heq\text{-}5}$=13.9, and $J_{Hax\text{-}5\text{–}Hax\text{-}6}$=ca. 11.2 Hz) and CH_{eq}-5 proton giving ddd (*J* 13.9, 5.6, 3.0 Hz) unequivocally indicated the equatorial position of the C-6 substituent in this case.

3. Conclusion

In conclusion, the efficient synthesis of 4-nitroalkyl-piperidino-2-thiones by Michael addition of nitroalkanes to α,β-unsaturated δ-thiolactams nonactivated by electron-withdrawing groups was described. For 6-substituted derivatives, highly diastereoselective additions were observed, for steric and electronic reasons. Hydrogen bond assistance was found to be responsible for complete diastereoselective addition to NH derivatives irrespective of the size of donor and substituent at C-6. The LUMO energy of α,β-unsaturated δ-thiolactam acceptors, dependent on the type of substituents at N-1 and C-6 is the factor influencing the reactivity of the addition. The direction of activation can be used to design new reactive acceptors. As revealed from a comparative study, the Michael additions of nitroalkanes to the corresponding lactams are less effective because of their low reactivity (high energy of LUMO). However, the successful synthesis of 4-nitroalkylpiperidin-2-ones from analogous δ-thiolactams indicated the way to overcome this problem. Finally, it should be emphasized that because of combined presence of both highly convertible nitroalkyl and thiolactam groups in 4-nitroalkylpiperidine-2-thione, the compounds obtained stands as valuable precursors in prospective synthesis of piperidine derivatives.

4. Experimental

4.1. General

All ^{1}H and ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with a 5 mm ^{1}H/BB-inverse probehead, operating at 400.13 and 100.62 MHz. TMS was used as internal reference. Two-dimensional spectra were acquired using standard Bruker software. In the ^{1}H–^{1}H NOESY experiments a mixing time of 0.75 s was used. Enhanced resolution spectra were obtained by using Bruker software. Yields determined by ^{1}H NMR spectra were obtained by using 1,3,5-trimethoxybenzene as internal reference. 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. The analytical procedure was developed on 30 m long capillary column, 0.2 mm in diameter, with methylsiloxane modified with phenyl groups (5% Ph, Me siloxane) in the 0.25 μm active phase layer. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Infrared spectra were taken with a Specord M80 instrument. Elemental analyses were performed on EuroEA 3000 series, EuroVector CHNS-O Elemental Analyzer. HRMS analyses were performed on Spektrometr AMD Intectra Mass AMD 402. Melting points were determined on a Boetius hot stage apparatus. Thiolactams **3a**,**b**, **3f**[29] and **3c**–**e**[25] were obtained according to the methods described earlier.

4.2. Addition of nitroalkanes to α,β-unsaturated δ-thiolactams. General procedure

α,β-Unsaturated δ-thiolactam **3**[†] (1.0 mmol) was dissolved in a solution of nitroalkane,[‡] and a catalytic amount of DBU (Tables 1–3) was added. In some cases, a small amount of acetonitrile was also added (Tables 1–3). The mixture was stirred at the temperature and time indicated in Tables 1–3. When the reaction was complete, 5 ml of concentrated NH_4Cl was added and the solution was extracted twice with ethyl acetate (2×50 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica (*n*-hexane/ethyl acetate=8:2 then 7:3)[§] and crystallized from the appropriate solvents.

4.2.1. 1-Methyl-4-nitromethylpiperidine-2-thione (**4a**)

Pale yellow oil (169 mg, 90%). IR (thin film): ν=2960, 2916, 1548, 1348, 1268, 1232, 1110, 1072, 796 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.68–1.81 (1H, m, CHH_{ax}-5), 2.14 (1H, dm, *J* ca. 11.4 Hz, CHH_{eq}-5), 2.65–2.75 (2H, m, C*H*H-3, CH-4), 3.25–3.36 (1H, m, CH*H*-3), 3.48 (3H, s, NCH_3), 3.57 (1H, ddd, *J* ca. 14.4, 10.4, 4.9 Hz, CHH_{ax}-6), 3.62 (1H, ddd, *J* ca. 14.2, 6.2, 3.3 Hz, CHH_{eq}-6), 4.30 (1H, dd, *J* 12.7, 7.9 Hz, C*H*HNO_2), 4.40 (1H, dd, *J* 12.7, 5.5 Hz, CH*H*NO_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=26.2 (CH_2-5), 31.4 (CH-4), 43.1 (NCH_3), 44.0 (CH_2-3), 51.8 (CH_2-6), 78.6 (CH_2NO_2), 196.0 (C-2); GC–MS (EI, 70 eV): *m*/*z*=188 (100, M$^{+\bullet}$), 154 (13), 142 (10), 128 (16), 99 (12), 82 (8), 69 (12), 55 (22), 44 (32), 42 (23), 41 (28); HRMS (EI) for $C_7H_{12}N_2O_2S$: calculated 188.0620, found 188.0619.

4.2.2. 4-Nitromethyl-1-phenylpiperidine-2-thione (**4b**)

Colorless solid (228 mg, 91%), mp 116–118 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2948, 2924, 1556, 1498, 1440, 1410, 1372, 1348, 1334, 1232, 1196, 1148, 1036, 868, 764, 740, 698 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.81–1.94 (1H, m, CHH_{ax}-5), 2.23 (1H, dm, *J* ca. 12.5 Hz, CHH_{eq}-5), 2.81–2.91 (2H, m, CH-4, CHH_{eq}-3), 3.45 (1H, ddd, *J* 12.8, 9.5, 2.0 Hz, CHH_{ax}-3), 3.72–3.85 (2H, m, CH_2-6), 4.38 (1H, dd, *J* 12.6, 7.7 Hz, C*H*HNO_2), 4.46 (1H, dd, *J* 12.6, 5.5 Hz,

[†] Instead of **3** their β,γ-unsaturated isomers can be used.

[‡] In the case of 2-nitropropane an argon atmosphere was used in order to prevent amide formation.

[§] If 4-nitroalkyl δ-thiolactams are hardly soluble, a mixture of eluent with a few ml of DMSO was used for dissolving the crude product and a so prepared solution was submitted for chromatographic column.

CH*H*NO_2), 7.21 (2H, d, *J* 7.2 Hz, C_6H_5), 7.40 (1H, t, *J* 7.4 Hz, C_6H_5), 7.48 (2H, d, *J* 7.4 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=26.4 (CH_2-5), 31.5 (CH-4), 44.6 (CH_2-3), 53.9 (CH_2-6), 78.8 (CH_2NO_2), 126.1, 128.3, 129.9, 146.2 (C_6H_5), 198.8 (C-2); GC–MS (EI, 70 eV): *m*/*z*=250 (63, $M^{+\bullet}$), 249 (100), 215 (15), 188 (14), 175 (38), 149 (16), 106 (11), 77 (20). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81%. Found: C, 57.54; H, 5.59; N, 11.23; S, 12.88%.

4.2.3. 1-Methyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**4c**)

Colorless solid (158 mg, 73%), mp 112–114 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2944, 1534, 1472, 1404, 1380, 1352, 1324, 1244, 1128, 1116, 1076 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.55 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.66 (1H, qd, *J* 11.9, 5.8 Hz, CHH_{ax}-5), 1.85 (1H, dm, *J* ca. 12.0 Hz, CHH_{eq}-5), 2.51 (1H, tdd, *J* 12.0, 4.4, 3.1 Hz, CH_{ax}-4), 2.68 (1H, dd, *J* 17.6, 12.1 Hz, CHH_{ax}-3), 3.22 (1H, ddd, *J* 17.6, 4.1, 3.1 Hz, CHH_{eq}-3), 3.46 (3H, s, NCH_3), 3.51 (1H, ddd, *J* 13.6, 12.1, 4.6 Hz, CHH_{ax}-6), 3.61 (1H, ddd, *J* 13.6, 5.8, 2.0 Hz, CHH_{eq}-6); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.2 (CH_3), 24.1 (CH_3), 24.3 (CH_2-5), 40.6 (CH-4), 42.4 (CH_2-3), 42.9 (NCH_3), 52.8 (CH_2-6), 90.0 (CNO_2), 196.7 (C-2); GC–MS (EI, 70 eV): *m*/*z*=216 (92, $M^{+\bullet}$), 188 (15), 170 (100), 128 (22), 102 (8), 55 (61). Anal. Calcd for $C_9H_{16}N_2O_2S$: C, 49.97; H, 7.46; N, 12.95; S, 14.82%. Found: C, 50.03; H, 7.49; N, 13.02; S, 14.89%.

4.2.4. 4-(1-Methyl-1-nitroethyl)-1-phenylpiperidine-2-thione (**4d**)

Colorless solid (228 mg, 82%), mp 195–197 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=1534, 1504, 1492, 1344, 1148, 772, 700 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.62 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.85 (1H, dtd, *J* 13.2, 11.4, 5.7 Hz, CHH_{ax}-5), 1.96 (1H, dm, *J* ca. 13.2 Hz, CHH_{eq}-5), 2.72 (1H, tdd, *J* ca. 11.6, 4.6, 3.7 Hz, CH_{ax}-4), 2.87 (1H, dd, *J* 17.6, 11.9 Hz, CHH_{ax}-3), 3.41 (1H, ddd, *J* 17.6, 4.6, 2.5 Hz, CHH_{eq}-3), 3.73 (1H, ddd, *J* 13.6, 11.3, 4.6 Hz, CHH_{ax}-6), 3.81 (1H, ddd, *J* 13.6, 5.7, 3.8 Hz, CHH_{eq}-6), 7.20 (2H, dm, *J* ca. 8.3 Hz, C_6H_5), 7.38 (1H, tt, *J* ca. 7.4, ca. 1.3 Hz, C_6H_5), 7.45–7.51 (2H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=20.2 (CH_3), 23.5 (CH_3), 23.6 (CH_2-5), 39.9 (CH-4), 42.2 (CH_2-3), 53.7 (CH_2-6), 89.2 (CNO_2), 125.1, 127.2, 128.9, 145.2 (C_6H_5), 198.7 (C-2); GC–MS (EI, 70 eV): *m*/*z*=278 (78, $M^{+\bullet}$), 277 (100), 248 (8), 232 (63), 230 (35), 217 (9), 188 (41), 175 (11), 150 (9), 119 (12), 106 (35), 104 (18), 77 (39), 55 (53), 41 (19). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.06; S, 11.52%. Found: C, 60.33; H, 6.59; N, 10.02; S, 11.56%.

4.2.5. 1-Methyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**4e**)

Colorless solid (246 mg, 96%), mp 125–127 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2932, 2860, 1536, 1448, 1428, 1352, 1224, 1092, 1076, 848 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.15–1.43 (3H, m, 3×C*H*H), 1.47–1.87 (6H, m, 3×CH*H*, 2×CCHH_{ax}, CHH_{ax}-5), 1.93 (1H, dm, *J* ca. 13.3 Hz, CHH_{eq}-5), 2.17 (1H, tdd, *J* 12.1, 4.7, 3.1 Hz, CH_{ax}-4), 2.45 (1H, dm, *J* 13.7 Hz, CCHH_{eq}), 2.49 (1H, dm, *J* 13.8 Hz, CCHH_{eq}), 2.73 (1H, dd, *J* 17.9, 12.1 Hz, CHH_{ax}-3), 3.30 (1H, ddd, *J* 17.9, 4.4, 2.8 Hz, CHH_{eq}-3), 3.40–3.50 (4H, m, CHH_{ax}-6, NCH_3), 3.58 (1H, ddd, *J* 13.7, 5.7, 2.1 Hz, CHH_{eq}-6); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0, 22.2 (2×CH_2), 24.0 (CH_2-5), 24.6 (CH_2), 29.9, 32.3 (2×CCH_2), 41.3 (CH-4), 42.4 (CH_2-3), 43.0 (NCH_3), 53.0 (CH_2-6), 93.4 (CNO_2), 197.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=256 (50, $M^{+\bullet}$), 226 (19), 210 (100), 128 (24), 102 (38), 44 (15). Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93; S, 12.51%. Found: C, 56.18; H, 7.89; N, 11.02; S, 12.56%.

4.2.6. 4-(1-Nitrocyclohexyl)-1-phenylpiperidine-2-thione (**4f**)

Colorless solid (229 mg, 72%), mp 165–167 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2928, 2860, 1528, 1500, 1450, 1348, 1252, 1148, 846, 756, 694 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.17–1.47 (3H, m, 3×C*H*H), 1.55–1.87 (6H, m, 3×CH*H*, 2×C*H*H, CHH_{ax}-5), 2.04 (1H, dm, *J* ca. 13.4 Hz, CHH_{eq}-5), 2.37 (1H, tdd, *J* ca. 11.7, 4.6, 3.8 Hz, CH_{ax}-4), 2.52 (1H, br d, *J* ca. 13.4 Hz, CH*H*), 2.55 (1H, br d, *J* ca. 13.5 Hz, CH*H*), 2.91 (1H, dd, *J* 17.8, 12.0 Hz, CHH_{ax}-3), 3.46 (1H, ddd, *J* 17.8, 4.7, 2.3 Hz, CHH_{eq}-3), 3.67 (1H, ddd, *J* 13.5, 12.0, 4.5 Hz, CHH_{ax}-6), 3.79 (1H, ddd, *J* 13.5, 5.5, 2.8 Hz, CHH_{eq}-6), 7.18 (2H, dm, *J* ca. 8.0 Hz, C_6H_5), 7.37 (1H, tt, *J* ca. 7.6, ca. 1.2 Hz, C_6H_5), 7.47 (2H, t, *J* ca. 8.0 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.1, 22.3 (2×CH_2), 24.2 (CH_2-5), 24.7, 30.1, 32.4 (3×CH_2), 41.5 (CH-4), 43.0 (CH_2-3), 54.8 (CH_2-6), 93.5 (CNO_2), 126.1, 128.2, 129.9, 146.3 (C_6H_5), 200.0 (C-2); GC–MS (EI, 70 eV): *m*/*z*=318 (<1, $M^{+\bullet}$), 271 (84), 270 (100), 268 (29), 256 (34), 238 (30), 207 (27), 190 (11), 176 (9), 162 (15), 106 (20), 91 (14), 77 (32). Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07%. Found: C, 64.18; H, 7.09; N, 8.82; S, 10.16%.

4.2.7. trans (T) and cis (C) 6-Allyl-1-methyl-4-nitromethylpiperidine-2-thione (**5a**:**6a**)

Unseparable mixture of diastereoisomers (T/C=1:1). Pale yellow oil (130 mg, 57%). IR (thin film): ν=3076, 2964, 1546, 1512, 1376 br, 1112 br, 1076, 924 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.55 (1H, ddd, *J* 13.5, 12.2, 10.1 Hz, CHH_{ax}-5 (C)), 1.70 (1H, tdd, *J* ca. 13.3, 5.6, 0.7 Hz, CHH_{ax}-5 (T)), 2.11 (1H, dq, *J* 13.4, 2.3 Hz, CHH_{eq}-5 (T)), 2.18 (1H, ddt, *J* 13.5, 6.7, 3.5 Hz, CHH_{eq}-5 (C)), 2.27–2.38 (1H, m, 6-C*H*H (T)), 2.45–2.65 (5H, m, CH_{ax}-4 (C), CHH_{ax}-3 (C), 6-CH_2 (C), 6-CH*H* (T)), 2.70 (1H, ddd, *J* 18.1, 11.0, 0.9 Hz, CHH_{ax}-3 (T)), 2.78–2.91 (1H, m, CH_{ax}-4 (T)), 3.28–3.38 (2H, m, 2×CHH_{eq}-3 (C, T)), 3.47 (3H, s, NCH_3 (C)), 3.49 (3H, s, NCH_3 (T)), 3.65–3.72 (1H, m, CH_{eq}-6 (T)), 3.72–3.79 (1H, m, CH_{ax}-6 (C)), 4.21–4.28 (2H, m, 2×C*H*HNO_2 (T, C)), 4.36 (1H, d, *J* 12.6 Hz, CH*H*NO_2 (T)), 4.37 (1H, d, *J* 12.8 Hz, CH*H*NO_2 (C)), 5.16–5.25 (4H, m, 2×=CH_2 (T, C)), 5.54–5.65 (1H, m, =CH (C)), 5.64–5.74 (1H, m, =CH (T)); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=27.5 (CH-4 (T)), 28.8 (CH_2-5 (T)), 30.3 (CH-4 (C)), 32.0 (CH_2-5 (C)), 36.9 (6-CH_2 (T)), 38.6 (6-CH_2 (C)), 41.0 (NCH_3 (C)), 43.0 (NCH_3 (T)), 43.7 (CH_2-3 (T)), 45.0 (CH_2-3 (C)), 60.9 (CH-6 (C)), 61.3 (CH-6 (T)), 78.8 (CH_2NO_2 (T, C)), 119.9 (=CH_2 (T)), 120.6 (=CH_2 (C)), 130.9 (=CH (C)), 132.4 (=CH (T)), 196.0 (C-2 (T)), 198.0 (C-2 (C)); GC–MS (EI, 70 eV): (C) *m*/*z*=228 (27, $M^{+\bullet}$), 198 (7), 187 (15), 140 (12), 126 (100), 84 (22), 67 (11), 55 (12), 41 (19); (T) *m*/*z*=228 (30, $M^{+\bullet}$), 198 (6), 187 (13), 140 (15), 126 (100), 84 (25), 67 (11), 55 (12), 41 (21); HRMS (EI) for $C_{10}H_{16}N_2O_2S$: calculated 228.0932, found 228.0929.

4.2.8. trans (T) and cis (C) 6-Allyl-1-benzyl-4-nitromethylpiperidine-2-thione (**5b**:**6b**)

Unseparable mixture of diastereoisomers (T/C=6:4). Pale yellow oil (289 mg, 95%). IR (thin film): ν=2944, 1548, 1496, 1452, 1340, 1176, 1108, 924, 728, 696 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.50 (1H, td, *J* ca. 12.5, 4.6 Hz, CHH_{ax}-5 (T)), 1.58 (1H, ddd, *J* 13.5, 11.1, 8.7 Hz, CHH_{ax}-5 (C)), 2.02–2.13 (2H, m, 2×CHH_{eq}-5 (T, C)), 2.29–2.51 (3H, m, 6-C*H*H, 2×6-CH*H* (T, C)), 2.55–2.65 (2H, m, 6-CHH (T)), 2.67 (1H, dd, *J* 16.4, 12.2 Hz, CHH_{ax}-3 (C)), 2.86 (1H, dd, *J* 17.9, 10.3 Hz, CHH_{ax}-3 (T)), 2.87–2.98 (1H, m, CH-4 (T)), 3.40–3.50 (2H, m, 2×CHH_{eq}-3 (T, C)), 3.60–3.69 (2H, m, 2×CH-6), 4.23 (1H, dd, *J* 12.3, 10.6 Hz, C*H*HNO_2 (C)), 4.25 (1H, dd, *J* 12.5, 10.4 Hz, C*H*HNO_2 (T)), 4.30–4.39 (2H, m, 2×CH*H*NO_2 (T, C)), 4.40 (1H, d, *J* 14.9 Hz, NC*H*H (T)), 4.49 (1H, d, *J* 15.0 Hz, NC*H*H (C)), 5.11–5.22 (4H, m, 2×=CH_2 (T, C)), 5.53–5.68 (2H, m, 2×=CH (T, C)), 6.46 (1H, d, *J* 14.9 Hz, NCH*H* (T)), 6.47 (1H, d, *J* 15.0 Hz, NCH*H* (C)), 7.21–7.40 (10H, m, 2×C_6H_5 (T, C)); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=27.4 (CH-4 (T)), 29.1 (CH_2-5 (T)), 30.4 (CH-4 (C)), 31.5 (CH_2-5 (C)), 36.5 (6-CH_2 (T)), 38.3 (6-CH_2 (C)), 43.8 (CH_2-3 (T)), 45.3 (CH_2-3 (C)), 54.0 (NCH_2 (C)), 55.2 (NCH_2 (T)), 57.1 (CH-6 (T)), 57.2 (CH-6 (C)), 79.0 (CH_2NO_2 (T, C)), 119.8 (=CH_2 (T)), 120.4 (=CH_2 (C)), 127.6, 127.7, 127.9, 128.0, 128.9, 128.9, 135.1, 135.2 (C_6H_5 (T, C)), 131.4 (=CH (C)), 132.5 (=CH (T)), 197.0 (C-2 (T)), 200.0 (C-2 (C)); GC–MS (EI, 70 eV): (C) *m*/*z*=304 (4, $M^{+\bullet}$), 303 (6), 213 (10), 148 (5), 131 (6), 106 (7), 91 (100), 65 (11), 41 (11); (T) *m*/*z*=304 (4, $M^{+\bullet}$), 303 (3), 213 (5), 148 (5), 131 (6), 106 (6), 91 (100), 65 (11), 41 (13); HRMS (EI) for $C_{16}H_{20}N_2O_2S$: calculated 304.1245, found 304.1248.

*4.2.9. trans 6-Allyl-4-nitromethyl-1-phenylpiperidine-2-thione (**5c**)*

Pale yellow oil (180 mg). IR (thin film): ν=3060, 2932, 1554, 1492, 1466, 1448, 1412, 1376, 1332, 1150, 1132, 922, 764, 698 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.88 (1H, ddd, *J* ca. 13.3, 11.8, 5.6 Hz, CHH_{ax}-5), 2.25 (1H, dq, *J* 13.3, 2.6 Hz, CHH_{eq}-5), 2.28–2.38 (1H, m, 6-C*H*H), 2.58 (1H, dm, *J* ca. 14.0 Hz, 6-CH*H*), 2.89 (1H, dd, *J* 18.0, 10.5 Hz, CHH_{ax}-3), 2.92–3.04 (1H, m, CH_{ax}-4), 3.50 (1H, ddd, *J* 18.0, 4.9, 1.9 Hz, CHH_{eq}-3), 3.97 (1H, dm, *J* 10.4 Hz, CH_{eq}-6), 4.32 (1H, dd, *J* 12.6, 8.2 Hz, C*H*HNO_2), 4.44 (1H, dd, *J* 12.6, 5.7 Hz, CH*H*NO_2), 5.08–5.16 (2H, m, =CH_2), 5.47–5.59 (1H, m, =CH), 7.19 (2H, dm, *J* ca. 8.0 Hz, C_6H_5), 7.40 (1H, tt, *J* ca. 7.5, ca. 1.3 Hz, C_6H_5), 7.46–7.52 (2H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=27.7 (CH-4), 28.8 (CH_2-5), 36.7 (6-CH_2), 44.4 (CH_2-3), 62.1 (CH-6), 78.8 (CH_2NO_2), 119.8 (=CH_2), 127.5, 128.4, 129.7, 144.9 (C_6H_5), 132.3 (=CH), 199.2 (C-2); GC–MS (EI, 70 eV): *m*/*z*=290 (94, $M^{+\bullet}$), 289 (96), 249 (29), 202 (11), 188 (100), 149 (15), 118 (16), 104 (16), 93 (15), 84 (20), 77 (45), 67 (12), 51 (10), 41 (17). HRMS (EI) for $C_{15}H_{18}N_2O_2S$: calculated 290.1089, found 290.1087.

*4.2.10. trans 4-Nitromethyl-1,6-diphenylpiperidine-2-thione (**5d**)*

Yellow semisolid (173 mg). IR (KBr pellet): ν=2928, 1554, 1492, 1464, 1446, 1410, 1348, 1146, 1116, 762, 696 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ=2.11 (1H, dm, *J* ca. 13.2 Hz, CHH_{eq}-5), 2.23 (1H, ddd, *J* 13.2, 12.0, 5.6 Hz, CHH_{ax}-5), 2.71–2.90 (1H, m, CH-4), 2.99 (1H, dd, *J* 18.8, 10.3 Hz, CHH_{ax}-3), 3.59 (1H, ddd, *J* 18.8, 6.0, 1.5 Hz, CHH_{eq}-3), 4.18–4.33 (2H, m, CH_2NO_2), 5.09 (1H, dd, *J* 5.6, 2.6 Hz, CH_{eq}-6), 7.01 (2H, dd, *J* 6.8, 1.5 Hz, C_6H_5), 7.10–7.35 (8H, m, 2×C_6H_5); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=27.3 (CH-4), 34.3 (CH_2-5), 44.4 (CH_2-3), 67.8 (CH-6), 79.0 (CH_2NO_2), 126.8, 126.9, 128.1, 128.4, 129.0, 129.5, 138.8, 146.0 (2×C_6H_5), 200.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=326 (56, $M^{+\bullet}$), 325 (100), 167 (11), 149 (16), 129 (22), 91 (16), 77 (20); HRMS (EI) for $C_{18}H_{18}N_2O_2S$: calculated 326.1089, found 326.1091.

*4.2.11. cis 4-Nitromethyl-1,6-diphenylpiperidine-2-thione (**6d**)*

White solid (85 mg), mp 222–226 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3036, 2924, 1554, 1492, 1464, 1444, 1410, 1312, 1224, 1148, 1114, 764, 696 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ=2.03 (1H, dt, *J* 13.9, ca. 11.2 Hz, CHH_{ax}-5), 2.46 (1H, ddd, *J* 13.9, 5.6, 3.0 Hz, CHH_{eq}-5), 2.84–3.04 (2H, m, CH-4, CHH_{ax}-3), 3.57 (1H, dd, *J* 13.2, 3.0 Hz, CHH_{eq}-3), 4.26 (1H, dd, *J* 12.3, 7.9 Hz, C*H*HNO_2), 4.39 (1H, dd, *J* 12.3, 5.6 Hz, CH*H*NO_2), 4.85 (1H, dd, *J* 10.7, 5.6 Hz, CH_{ax}-6), 6.83 (2H, dd, *J* 7.1, 1.5 Hz, C_6H_5), 7.00–7.20 (8H, m, 2C_6H_5); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=31.6 (CH-4), 36.4 (CH_2-5), 45.8 (CH_2-3), 68.8 (CH-6), 127.7, 127.7, 127.8, 128.5, 128.9, 129.1, 139.1, 144.4 (2×C_6H_5), 200.5 (C-2); GC–MS (EI, 70 eV): *m*/*z*=326 (56, $M^{+\bullet}$), 325 (100), 167 (11), 149 (16), 129 (22), 91 (16), 77 (20); HRMS (EI) for $C_{18}H_{18}N_2O_2S$: calculated 326.1089, found 326.1090.

*4.2.12. trans 6-Allyl-1-methyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**5e**)*

Colorless solid (177 mg, 69%), mp 92–94 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3076, 2992, 2972, 2948, 2872, 1528, 1402, 1358, 1244, 1220, 1124, 1106, 1068, 1052, 996, 930, 852 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.53 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.58–1.69 (1H, m, CHH_{ax}-5), 1.89 (1H, dm, *J* ca. 13.4 Hz, CHH_{eq}-5), 2.24–2.34 (1H, m, 6-C*H*H), 2.61 (1H, dm, *J* ca. 14.0 Hz, 6-CH*H*), 2.66–2.77 (2H, m, C*H*H-3, CH_{ax}-4), 3.20–3.32 (1H, m, CH*H*-3), 3.47 (3H, s, NCH_3), 3.65 (1H, dddd, *J* 10.5, ca. 5.6, 4.1, 1.6 Hz, CH_{eq}-6), 5.15–5.23 (2H, m, =CH_2), 5.59–5.71 (1H, m, =CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=20.9 (CH_3), 24.1 (CH_3), 26.5 (CH_2-5), 36.1 (CH-4), 36.6 (6-CH_2), 42.3 (CH_2-3), 43.0 (NCH_3), 61.9 (CH-6), 90.1 (CNO_2), 119.9 (=CH_2), 132.6 (=CH), 196.8 (C-2); GC–MS (EI, 70 eV): *m*/*z*=256 (14, $M^{+\bullet}$), 226 (6), 210 (13), 168 (57), 154 (29), 126 (49), 111 (26), 97 (44), 95 (26), 81 (23), 79 (24), 77 (22), 69 (34), 67 (37), 55 (42), 53 (25), 42 (73), 41 (100), 39 (34). Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93; S, 12.51%. Found: C, 56.30; H, 7.95; N, 10.90; S, 12.39%.

*4.2.13. trans 6-Allyl-1-benzyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**5f**)*

Colorless solid (299 mg, 90%), mp 124–126 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2976, 1534, 1508, 1348, 1178, 920, 740 cm^{-1}; ^1H NMR (400.1 MHz, toluene-d_8): δ=0.75 (1H, td, *J* 12.8, 5.2 Hz, CHH_{ax}-5), 0.87 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.16 (1H, dm, *J* ca. 12.9 Hz, CHH_{eq}-5), 1.71 (1H, dt, *J* 14.0, ca. 9.4 Hz, 6-C*H*H), 2.02 (1H, dm, *J* ca. 14.0, 6-CH*H*), 2.33 (1H, dddd, *J* 12.8, 11.0, 6.0, 3.2 Hz, CH_{ax}-4), 2.52 (1H, dd, *J* 18.3, 11.0 Hz, CHH_{ax}-3), 3.02–3.09 (1H, m, CH_{eq}-6), 3.10 (1H, ddd, *J* 18.3, 6.0, 1.3 Hz, CHH_{eq}-3), 3.94 (1H, d, *J* 14.6 Hz, NC*H*H), 4.84–4.92 (2H, m, =CH_2), 5.07–5.20 (1H, m, =CH), 6.47 (1H, d, *J* 14.6 Hz, NCH*H*), 6.95–7.14 (4H, m, C_6H_5), 7.20 (1H, d, *J* 7.3 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, toluene-d_8): δ=19.9 (CH_3), 24.0 (CH_3), 26.9 (CH_2-5), 35.9 (6-CH_2), 36.3 (CH-4), 42.8 (CH_2-3), 54.7 (NCH_2), 57.3 (CH-6), 90.0 (CNO_2), 118.9 (=CH_2), 128.0, 128.42, 128.9, 136.6 (C_6H_5), 133.4 (=CH), 198.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=332 (6, $M^{+\bullet}$), 302 (6), 286 (9), 244 (12), 91 (100), 41 (16). Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43; S, 9.65%. Found: C, 64.92; H, 7.22; N, 8.49; S, 9.77%.

*4.2.14. trans 6-Allyl-4-(1-methyl-1-nitroethyl)-1-phenyl-piperidine-2-thione (**5g**)*

White solid (280 mg, 88%), mp 179–181 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2988, 1538, 1494, 1470, 1450, 1400, 1376, 1346, 1260, 1248, 1152, 1060, 928, 852, 768, 700 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.59 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.81 (1H, td, *J* 13.1, 5.6 Hz, CHH_{ax}-5), 2.00 (1H, dq, *J* 13.1, ca. 2.4 Hz, CHH_{eq}-5), 2.33 (1H, ddd, *J* 13.9, 10.9, 9.0 Hz, 6-C*H*H), 2.58 (1H, dm, *J* ca. 13.9 Hz, 6-CH*H*), 2.80–2.94 (2H, m, C*H*H-3, CH_{ax}-4), 3.39–3.47 (1H, m, CH*H*-3), 3.94 (1H, dddd, *J* 11.0, 5.6, 4.0, 1.8 Hz, CH_{eq}-6), 5.06–5.14 (2H, m, =CH_2), 5.41–5.52 (1H, m, =CH), 7.18 (2H, dd, *J* 8.5, 1.3 Hz, C_6H_5), 7.40 (1H, tt, *J* 7.5, 1.1 Hz, C_6H_5), 7.49 (2H, t, *J* 7.9 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.1 (CH_3), 24.4 (CH_3), 26.4 (CH_2-5), 36.2 (CH-4), 36.3 (6-CH_2), 43.1 (CH_2-3), 62.7 (CH-6), 90.1 (CNO_2), 119.8 (=CH_2), 127.5 (br), 128.3, 129.7, 144.9 (C_6H_5), 132.4 (=CH), 200.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=318 (27, $M^{+\bullet}$), 317 (23), 272 (18), 230 (37), 216 (20), 188 (49), 186 (18), 172 (16), 105 (34), 97 (54), 77 (100), 69 (51), 55 (30), 51 (28), 41 (75). Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07%. Found: C, 64.05; H, 6.99; N, 8.90; S, 9.99%.

*4.2.15. trans 4-(1-Methyl-1-nitroethyl)-1,6-diphenyl-piperidine-2-thione (**5h**)*

White solid (266 mg, 75%), mp 205–207 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3064, 2940, 1594, 1534, 1492, 1468, 1444, 1346, 1148, 852, 764, 696, 592 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.53 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.99 (1H, dm, *J* 12.9 Hz, CHH_{eq}-5), 2.24 (1H, td, *J* 12.9, 5.4 Hz, CHH_{ax}-5), 2.70 (1H, dddd, *J* 12.9, 11.1, 6.2, 3.2 Hz, CH_{ax}-4), 3.06 (1H, dd, *J* 18.9, 11.1 Hz, CHH_{ax}-3), 3.53 (1H, ddd, *J* 18.9, 6.2, 1.9 Hz, CHH_{eq}-3), 5.19 (1H, dd, *J* 5.4, 2.2 Hz, CH_{eq}-6), 7.10–7.15 (2H, m, C_6H_5), 7.19–7.23 (2H, m, C_6H_5), 7.24–7.42 (6H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.9 (CH_3), 23.9 (CH_3), 32.5 (CH_2-5), 36.1 (CH-4), 42.7 (CH_2-3), 67.6 (CH-6), 89.9 (CNO_2), 126.6, 126.8, 128.1, 128.3, 128.9, 129.5, 138.6, 146.1 (2×C_6H_5), 201.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=354 (62, $M^{+\bullet}$), 353 (100), 308 (22), 264 (32), 180 (11), 168 (13), 157 (19), 129 (16), 117 (14), 91 (27), 77 (24). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05%. Found: C, 67.81; H, 6.33; N, 7.96; S, 9.12%.

*4.2.16. trans 6-Allyl-1-methyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**5i**)*

White solid (112 mg, 38%), mp 135–137 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2944, 1528, 1448, 1352, 1072, 1048,

932 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.15–1.43 (3H, m, 3×C*H*H), 1.49–1.62 (3H, m, 2×CHH_{ax}, CHH_{ax}-5), 1.62–1.75 (3H, m, 3×CH*H*), 1.94 (1H, dq, *J* 13.5, ca. 2.3 Hz, CHH_{eq}-5), 2.20 (1H, dt, *J* 14.0, 9.6 Hz, 6-C*H*H), 2.33 (1H, tdd, *J* ca. 13.0, 5.5, ca. 2.4 Hz, CH_{ax}-4), 2.42 (1H, dm, *J* ca. 14.0 Hz, CHH_{eq}), 2.47 (1H, dm, *J* ca. 14.0 Hz, CHH_{eq}), 2.59 (1H, dm, *J* 14.0 Hz, 6-CH*H*), 2.80 (1H, ddd, *J* 18.4, 11.8, ca. 0.8 Hz, CHH_{ax}-3), 3.29 (1H, ddd, *J* 18.4, 5.4, 2.4 Hz, CHH_{eq}-3), 3.45 (3H, s, NCH_3), 3.65 (1H, dm, *J* ca. 10.3 Hz, CH_{eq}-6), 5.14 (1H, dq, *J* 17.0, ca. 1.2 Hz, =C*H*H), 5.19 (1H, dm, *J* 10.2 Hz, =CH*H*), 5.57–5.69 (1H, m, =CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0, 22.2, 24.6 (3×CH_2), 26.1 (CH_2-5), 29.8, 32.2 (2×CH_2), 36.7 (CH-4, 6-CH_2), 42.1 (CH_2-3), 42.9 (NCH_3), 61.8 (CH-6), 93.3 (CNO_2), 119.7 (=CH_2), 132.6 (=CH), 197.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=296 (60, $M^{+\bullet}$), 266 (50), 250 (98), 208 (100), 168 (50), 150 (15), 126 (64), 91 (27), 79 (28), 67 (37), 55 (23), 41 (31). Anal. Calcd for $C_{15}H_{24}N_2O_2S$: C, 60.78; H, 8.16; N, 9.45; S, 10.82%. Found: C, 60.84; H, 8.03; N, 9.53; S, 10.90%.

4.2.17. *trans* 6-Allyl-1-benzyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**5j**)

White solid (231 mg, 62%), mp 106–108 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2936, 1528, 1504, 1452, 1346, 1170, 932, 704 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.17–1.43 (4H, m, 3×C*H*H, CHH_{ax}-5), 1.48–1.61 (2H, m, 2×C*H*H), 1.62–1.76 (3H, m, 3×CH*H*), 1.89 (1H, dq, *J* 13.3, 2.4 Hz, CHH_{eq}-5), 2.16–2.32 (1H, m, 6-C*H*H), 2.36–2.52 (3H, m, 2×CH*H*, CH-4), 2.59 (1H, dm, *J* ca. 14.1 Hz, 6-CH*H*), 2.96 (1H, dd, *J* 18.7, 11.1 Hz, CHH_{ax}-3), 3.38 (1H, ddm, *J* 18.7, ca. 6.0 Hz, CHH_{eq}-3), 3.57–3.65 (1H, m, CH_{eq}-6), 4.37 (1H, d, *J* 14.9 Hz, NC*H*H), 5.08–5.18 (2H, m, =CH_2), 5.50–5.61 (1H, m, =CH), 6.42 (1H, d, *J* 14.9 Hz, NCH*H*), 7.23–7.37 (5H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0, 22.2, 24.6 (3×CH_2), 26.5 (CH_2-5), 29.9, 32.1 (2×CH_2), 36.3 (6-CH_2), 36.7 (CH-4), 42.2 (CH_2-3), 55.1 (NCH_2), 57.4 (CH-6), 93.4 (CNO_2), 119.5 (=CH_2), 127.6, 127.9, 128.9, 135.1 (C_6H_5), 132.7 (=CH), 198.6 (C-2); GC–MS (EI, 70 eV): *m*/*z*=372 (<1, $M^{+\bullet}$), 325 (59), 310 (10), 292 (40), 282 (15), 234 (22), 151 (14), 117 (18), 91 (100), 79 (16), 65 (11), 41 (10). Anal. Calcd for $C_{21}H_{28}N_2O_2S$: C, 67.71; H, 7.58; N, 7.52; S, 8.61%. Found: C, 67.80; H, 7.56; N, 7.59; S, 8.55%.

4.2.18. *trans* 6-Allyl-4-(1-nitrocyclohexyl)-1-phenylpiperidine-2-thione (**5k**)

White solid (233 mg, 65%), mp 179–181 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=2936, 2868, 1530, 1494, 1472, 1450, 1338, 1150, 1136, 932, 844, 764, 696 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.17–1.46 (3H, m, 3×C*H*H), 1.53–1.65 (2H, m, 2×C*H*H), 1.65–1.81 (4H, m, 3×CH*H*, CHH_{ax}-5), 2.11 (1H, ddd, *J* 13.4, 2.3, 2.0 Hz, CHH_{eq}-5), 2.25 (1H, ddd, *J* 13.9, ca. 11.0, ca. 10.0 Hz, 6-C*H*H), 2.42–2.61 (4H, m, 6-CH*H*, 2×CH*H*, CH_{ax}-4), 2.98 (1H, dd, *J* 18.7, 11.7 Hz, CHH_{ax}-3), 3.45 (1H, ddd, *J* 18.7, 5.4, 2.4 Hz, CHH_{eq}-3), 3.93 (1H, dm, *J* ca. 10.8 Hz, CH_{eq}-6), 5.07 (1H, br d, *J* 17.1 Hz, =C*H*H), 5.12 (1H, br d, *J* ca. 10.1 Hz, =CH*H*), 5.40–5.52 (1H, m, =CH), 7.15 (2H, dm, *J* ca. 7.3 Hz, C_6H_5), 7.39 (1H, tt, *J* ca. 7.3, 1.3 Hz, C_6H_5), 7.48 (2H, t, *J* 8.0 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.1, 22.3, 24.7 (3×CH_2), 26.2 (CH_2-5), 30.1, 32.2 (2×CH_2), 36.4 (6-CH_2), 36.7 (CH-4), 42.8 (CH_2-3), 62.5 (CH-6), 93.4 (CNO_2), 119.6 (=CH_2), 127.5 br, 128.3, 129.7, 144.9 (C_6H_5), 132.6 (=CH), 200.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=358 (<1, $M^{+\bullet}$), 311 (100), 310 (54), 278 (27), 270 (33), 268 (43), 216 (13), 204 (18), 190 (9), 151 (34), 135 (11), 117 (33), 104 (15), 91 (27), 77 (50), 41 (15). Anal. Calcd for $C_{20}H_{26}N_2O_2S$: C, 67.01; H, 7.31; N, 7.81; S, 8.94%. Found: C, 67.00; H, 7.40; N, 7.69; S, 9.04%.

4.2.19. *trans* 4-(1-Nitrocyclohexyl)-1,6-diphenylpiperidine-2-thione (**5l**)

White solid (248 mg, 63%), mp 239–242 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3028, 2936, 2868, 1534, 1492, 1472, 1448, 1344, 1238, 844, 766, 700 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.10–1.43 (4H, m, CH_2, C*H*H, CHH_{ax}), 1.46–1.70 (4H, m, CH_2, CH*H*, CHH_{ax}), 2.09 (1H, dm, *J* ca. 13.1 Hz, CHH_{eq}-5), 2.16 (1H, td, *J* 13.1, 5.1 Hz, CHH_{ax}-5), 2.31–2.48 (3H, m, 2×CHH_{eq}, CH_{ax}-4), 3.14 (1H, dd, *J* 19.0, 11.2 Hz, CHH_{ax}-3), 3.57 (1H, ddd, *J* 19.0, 5.9, 1.7 Hz, CHH_{eq}-3), 5.17 (1H, dd, *J* ca. 4.9, ca. 2.4 Hz, CH_{eq}-6), 7.10 (2H, dm, *J* ca. 7.2 Hz, C_6H_5), 7.20 (2H, dm, *J* ca. 7.0 Hz, C_6H_5), 7.23–7.41 (6H, m, 2×C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.0, 22.1, 24.5, 30.6, 32.1 (5×CH_2), 32.2 (CH_2-5), 36.0 (CH-4), 42.2 (CH_2-3), 67.6 (CH-6), 92.8 (CNO_2), 126.6, 126.8, 128.1, 128.2, 128.9, 129.4, 138.9, 146.2 (2×C_6H_5), 201.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=394 (<1, $M^{+\bullet}$), 347 (100), 346 (65), 332 (12), 314 (50), 252 (58), 238 (13), 197 (27), 180 (15), 117 (15), 103 (20), 91 (49), 79 (25), 77 (42). Anal. Calcd for $C_{23}H_{26}N_2O_2S$: C, 70.02; H, 6.64; N, 7.10; S, 8.13%. Found: C, 70.09; H, 6.60; N, 7.19; S, 8.04%.

4.2.20. *trans* 6-Ethyl-4-nitromethylpiperidine-2-thione (**7a**)

White solid (162 mg, 80%), mp 106–108 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3176 br, 3060, 2956, 1550, 1352, 1340, 1200, 1136, 1074 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.01 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.60 (1H, dquartet, *J* 14.0, 7.4 Hz, C*H*HCH$_3$), 1.71 (1H, dquartet, *J* 14.0, 7.4 Hz, CH*H*CH$_3$), 1.78–1.84 (2H, m, CH_2-5), 2.68 (1H, dd, *J* 18.1, 8.1 Hz, CHH_{ax}-3), 2.75–2.86 (1H, m, CH-4), 3.13 (1H, dd, *J* 18.1, 5.0 Hz, CHH_{eq}-3), 3.49 (1H, dquintet, *J* ca. 6.3, ca. 2.5 Hz, CH-6), 4.34 (1H, dd *J* 12.5, 8.4 Hz, C*H*HNO$_2$), 4.41 (1H, dd, *J* 12.5, 6.4 Hz, CH*H*NO$_2$), 8.42 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=10.0 (CH_3), 28.2 (CH_2-5), 28.5 (CH-4), 28.5 (CH_2CH_3), 41.9 (CH_2-3), 54.4 (CH-6), 78.3 (CH_2NO_2), 199.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=202 (100, $M^{+\bullet}$), 173 (8), 140 (15), 126 (11), 112 (80), 96 (11), 84 (13), 58 (20), 55 (25), 41 (19). Anal. Calcd for $C_8H_{14}N_2O_2S$: C, 47.50; H, 6.98; N, 13.85; S, 15.85%. Found: C, 47.55; H, 7.03; N, 13.92; S, 15.83%.

4.2.21. *trans* 6-Butyl-4-nitromethylpiperidine-2-thione (**7b**)

White solid (202 mg, 88%), mp 110–112 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3172 br, 3064, 2952, 2860, 1548, 1338, 1132 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.87–0.98 (3H, m, CH_3), 1.27–1.40 (4H, m, 2×CH_2), 1.50–1.58 (1H, m, C*H*H), 1.59–1.73 (1H, m, CH*H*), 1.75–1.83 (2H, m, CH_2-5), 2.66 (1H, dd, *J* 18.1, 8.4 Hz, CHH_{ax}-3), 2.75–2.87 (1H, m, C*H*$_{ax}$-4), 3.12 (1H, dd, *J* 18.1, 4.9 Hz, CHH_{eq}-3), 3.50–3.64 (1H, m, CH_{eq}-6), 4.35 (1H, dd, *J* 12.5, 8.1 Hz, C*H*HNO$_2$), 4.41 (1H, dd, *J* 12.5, 6.4 Hz, CH*H*NO$_2$), 9.03 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH_3), 22.4 (CH_2), 28.5 (CH-4), 28.7 (CH_2-5), 35.3 (CH_2), 41.9 (CH_2-3), 53.1 (CH-6), 78.4 (CH_2NO_2), 199.1 (C-1); GC–MS (EI, 70 eV): *m*/*z*=230 (58, $M^{+\bullet}$), 184 (14), 140 (12), 126 (16), 112 (100), 100 (13), 84 (22), 69 (41). Anal. Calcd for $C_{10}H_{18}N_2O_2S$: C, 52.15; H, 7.88; N, 12.16; S, 13.92%. Found: C, 52.05; H, 7.93; N, 12.22; S, 13.83%.

4.2.22. *trans* 6-Hexyl-4-nitromethylpiperidine-2-thione (**7c**)

White solid (204 mg, 79%), mp 68–70 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3156, 3056, 2952, 2928, 2860, 1552, 1338, 1136 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.89 (3H, t, *J* 7.1 Hz, CH_3), 1.22–1.43 (8H, m, 4×CH_2), 1.48–1.60 (1H, m, C*H*H-5), 1.61–1.74 (1H, m, CH*H*-5), 1.77–1.86 (2H, m, CH_2), 2.66 (1H, dd, *J* 18.1, 8.2 Hz, CHH_{ax}-3), 2.75–2.86 (1H, m, CH-4), 3.13 (1H, dd, *J* 18.1, 5.0 Hz, CHH_{eq}-3), 3.51–3.60 (1H, dquintet, *J* ca. 2.6, ca. 6.4 Hz, CH-6), 4.34 (1H, dd, *J* 12.5, 8.3 Hz, C*H*HNO$_2$), 4.40 (1H, dd, *J* 12.5, 6.3 Hz, CH*H*NO$_2$), 8.70 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.03 (CH_3), 22.5 (CH_2), 25.6 (CH_2), 28.6 (CH-4), 28.8 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 35.7 (CH_2-5), 41.9 (CH_2-3), 53.1 (CH-6), 78.3 (CH_2NO_2), 199.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=258 (18, $M^{+\bullet}$), 228 (21), 212 (15), 196 (10), 183 (8), 164 (9), 153 (18), 140 (14), 125 (18), 112 (100), 100 (69), 84 (30), 69 (22), 55 (23), 41 (29). Anal. Calcd for $C_{12}H_{22}N_2O_2S$: C, 55.78; H, 8.58; N, 10.84; S, 12.41%. Found: C, 55.66; H, 8.64; N, 10.82; S, 12.33%.

4.2.23. *trans* 6-tert-Butyl-4-nitromethylpiperidine-2-thione (**7d**)

White solid (179 mg, 78%), mp 112–114 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3200, 2968, 1552, 1376, 1324, 1130,

1044 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.00 (9H, s, $C(CH_3)_3$), 1.80–1.86 (2H, m, CH_2-5), 2.80–2.87 (1H, m, $CH H_{ax}$-3), 2.86–2.93 (1H, m, CH_{ax}-4), 3.01 (1H, dd, *J* 17.3, 4.7 Hz, $CH H_{eq}$-3), 3.25 (1H, ddd, *J* 8.7, 6.8, 1.5 Hz, CH_{eq}-6), 4.38 (1H, dd, *J* 12.3, 8.9 Hz, $CH HNO_2$), 4.44 (1H, dd, *J* 12.3, 6.2 Hz, $CH HNO_2$), 8.07 (1H, NH, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=24.3 (CH_2-5), 25.7 ($C(CH_3)_3$), 29.7 (CH-4), 34.4 ($C(CH_3)_3$), 41.5 (CH_2-3), 60.7 (CH-6), 77.4 (CH_2NO_2), 201.0 (C-2); GC–MS (EI, 70 eV): *m*/*z*=230 (83, $M^{+\bullet}$), 173 (18), 154 (9), 126 (13), 112 (100), 100 (31), 84 (21), 69 (18), 57 (15), 41 (23). Anal. Calcd for $C_{10}H_{18}N_2O_2S$: C, 52.15; H, 7.88; N, 12.16; S, 13.92%. Found: C, 52.06; H, 7.93; N, 12.22; S, 13.83%.

4.2.24. *trans* 4-Nitromethyl-6-phenylpiperidine-2-thione (**7e**)

White solid (100 mg, 40%), mp 97–99 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3450 br, 3180 br, 3052, 1552, 1448, 1340, 1120, 760, 704 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=2.03–2.09 (2H, m, CH_2-5), 2.63–2.73 (1H, m, CH-4), 2.75 (1H, dd, *J* 18.2, 9.0 Hz, $CH H_{ax}$-3), 3.26 (1H, dd, *J* 18.2, 4.6 Hz, $CH H_{eq}$-3), 4.34 (2H, d, *J* 6.8 Hz, CH_2NO_2), 4.82 (1H, td, *J* 5.3, 3.1 Hz, CH_{eq}-6), 7.22 (2H, br d, *J* 7.2 Hz, C_6H_5), 7.35 (1H, tt, *J* 7.1, ca. 1.4 Hz, C_6H_5), 7.38–7.44 (2H, m, C_6H_5), 8.69 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=27.7 (CH-4), 32.4 (CH_2-3), 42.1 (CH_2-3), 57.0 (CH-6), 78.4 (CH_2NO_2), 126.3, 128.6, 129.3, 139.8 (C_6H_5), 200.6 (C-2); GC–MS (EI, 70 eV): *m*/*z*=250 (100, $M^{+\bullet}$), 216 (12), 203 (41), 202 (40), 188 (20), 175 (13), 156 (28), 131 (19), 129 (32), 117 (14), 115 (18), 106 (35), 104 (31), 91 (44), 77 (22). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81%. Found: C, 57.56; H, 5.63; N, 11.27; S, 12.83%.

4.2.25. *trans* 6-Allyl-4-nitromethylpiperidine-2-thione (**7f**)

White solid (137 mg, 64%), mp 83–85 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3156, 3072, 2964, 1576, 1548, 1444, 1430, 1408, 1376, 1348, 1264, 1144, 1042, 996, 924, 876 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.77–1.90 (2H, m, CH_2-5), 2.28–2.42 (2H, m, 6-CH_2), 2.70 (1H, dd, *J* 18.1, 7.7 Hz, $CH H_{ax}$-3), 2.83 (1H, m, CH-4), 3.14 (1H, dd, *J* 18.1, 5.0 Hz, $CH H_{eq}$-3), 3.62 (1H, m, CH_{eq}-6), 4.35 (1H, dd, *J* 12.5, 8.5 Hz, $CH HNO_2$), 4.41 (1H, dd, *J* 12.5, 6.2 Hz, $CH HNO_2$), 5.20–5.31 (2H, m, =CH_2), 5.68–5.81 (1H, m, =CH), 8.31 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=28.4 (CH_2-5), 28.5 (CH-4), 39.9 (6-CH_2), 41.9 (CH_2-3), 52.0 (CH-6), 78.1 (CH_2NO_2), 120.5 (=CH_2), 132.0 (=CH), 199.6 (C-2); GC–MS (EI, 70 eV): *m*/*z*=214 (46, $M^{+\bullet}$) 173 (21), 126 (8), 112 (100), 84 (21), 67 (9), 41 (14); HRMS (EI) for $C_9H_{14}N_2O_2S$: calculated 214.0776, found 214.0774.

4.2.26. *trans* 6-Ethyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**7g**)

White solid (207 mg, 90%), mp 184–186 °C from *n*-hexane. IR (KBr pellet): ν=3180 br, 3068, 2988, 2964, 2944, 2876, 1564, 1542, 1396, 1372, 1352, 1146, 1116, 1052, 1040, 874, 838 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.97 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.55 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.49–1.77 (4H, m, CH_2CH_3, CH_2-5), 2.56 (1H, dd, *J* 16.1, 12.2 Hz, $CH H_{ax}$-3), 2.54–2.65 (1H, m, CH_{ax}-4), 3.11 (1H, br d, *J* 16.1 Hz, $CH H_{eq}$-3), 3.55 (1H, dquintet, *J* ca. 7.0, ca. 3.4 Hz, CH_{eq}-6), 8.91 (1H, s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=10.5 (CH_2CH_3), 21.2 (CH_3), 24.6 (CH_3), 26.3 (CH_2CH_3), 28.1 (CH_2-5), 36.8 (CH-4), 41.1 br (CH_2-3), 55.7 (CH-6), 90.2 (CNO_2), 200.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=230 (100, $M^{+\bullet}$), 207 (6), 184 (62), 168 (16), 154 (15), 142 (12), 112 (22), 100 (17), 83 (20), 69 (48), 58 (19), 55 (25), 41 (28). Anal. Calcd for $C_{10}H_{18}N_2O_2S$: C, 52.15; H, 7.88; N, 12.16; S, 13.92%. Found: C, 52.06; H, 7.93; N, 12.22; S, 13.83%.

4.2.27. *trans* 6-Butyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**7h**)

White solid (227 mg, 88%), mp 120–121 °C from *n*-hexane. IR (KBr pellet): ν=3172 br, 3064, 2932, 2860, 1568, 1568, 1538, 1344, 1112 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.92 (3H, t, *J* 7.1 Hz, CH_3), 1.24–1.39 (4H, m 2×CH_2), 1.42–1.72 (4H, m, CH_2, CH_2-5), 1.55 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.55 (1H, dd, *J* 16.5, 12.1 Hz, $CH H_{ax}$-3), 2.55–2.65 (1H, m, CH_{ax}-4), 3.09 (1H, dd, *J* 16.1, ca. 3.1 Hz, $CH H_{eq}$-3), 3.55 (1H, dquintet, *J* ca. 7.4, ca. 3.4 Hz, CH_{eq}-6), 9.13 (1H, s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH_3), 21.3 (CH_3), 22.4 (CH_2), 24.5 (CH_3), 26.8 (CH_2), 28.1 (CH_2-5), 34.8 (CH-4), 40.9 (CH_2-3), 54.3 (CH-6), 90.2 (CNO_2), 200.0 (C-2); GC–MS (EI, 70 eV): *m*/*z*=258 ($M^{+\bullet}$,79), 228 (22), 212 (100), 170 (32), 168 (22), 154 (36), 128 (18), 112 (33), 97 (27), 86 (21), 83 (28), 69 (50), 55 (33), 41 (24). Anal. Calcd for $C_{12}H_{22}N_2O_2S$: C, 55.78; H, 8.58; N, 10.84; S, 12.41%. Found: C, 55.75; H, 8.39; N, 10.81; S, 12.40%.

4.2.28. *trans* 6-Hexyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**7i**)

White solid (209 mg, 73%), mp 112–114 °C from *n*-hexane. IR (KBr pellet): ν=3176 br, 3088, 2928, 2860, 1556, 1536, 1400, 1376, 1348, 1118 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.89 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.24–1.39 (8H, m, 4×CH_2), 1.45–1.73 (4H, m, CH_2-5, CH_2), 1.55 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.54 (1H, dd, *J* 16.5, 12.0 Hz, $CH H_{ax}$-3), 2.58–2.66 (1H, m, CH_{ax}-4), 3.08 (1H, br d, *J* 16.5 Hz, $CH H_{eq}$-3), 3.44–3.55 (1H, dquintet, *J* ca. 3.9, ca. 7.1 Hz, CH_{eq}-6), 9.31 (1H, s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.0 (CH_3), 21.3 (CH_3), 22.5 (CH_3), 24.5, 25.9, 26.8, 28.9, 31.5, 35.1 (6×CH_2), 36.7 (CH-4), 40.5 (CH_2-3), 54.5 (CH-6), 90.1 (CNO_2), 199.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=286 (28, $M^{+\bullet}$), 256 (47), 240 (100), 206 (15), 198 (51), 181 (46), 168 (21), 156 (18), 154 (38), 144 (10), 128 (51), 114 (26), 113 (36), 113 (136), 112 (41), 97 (26), 95 (22), 83 (24), 69 (58), 55 (42), 43 (28), 41 (41). Anal. Calcd for $C_{14}H_{26}N_2O_2S$: C, 58.70; H, 9.15; N, 9.78; S, 11.19%. Found: C, 58.66; H, 8.99; N, 9.77; S, 11.14%.

4.2.29. *trans* 6-tert-Butyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**7j**)

Colorless solid (222 mg, 86%), mp 157–159 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3248 br, 2964, 1526, 1478, 1400, 1380, 1352, 1336, 1312, 1248, 1142, 1058, 1028, 852, 708 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.00 (9H, s, $C(CH_3)_3$), 1.55 (3H, s, CH_3), 1.57–1.66 (4H, m, CH_3, $CH H_{ax}$-5), 1.75 (1H, dtd, *J* 14.0, ca. 5.9, 1.8 Hz, $CH H_{eq}$-5), 2.48 (1H, dd, *J* 16.2, 11.8 Hz, $CH H_{ax}$-3), 2.60 (1H, dddd, *J* 13.9, 11.8, 6.0, 4.1 Hz, CH_{ax}-4), 3.13 (1H, ddd, *J* 16.2, 4.1, 1.7 Hz, $CH H_{eq}$-3), 3.20 (1H, ddd, *J* 8.4, 5.8, 2.6 Hz, CH_{eq}-6), 8.18 (1H, s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.1 (CH_3), 23.6 (CH_2-5), 25.3 (CH_3), 26.3 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 38.3 (CH-4), 40.7 (CH_2-3), 62.2 (CH-6), 90.4 (CNO_2), 202.4 (C-2); GC–MS (EI, 70 eV): *m*/*z*=258 (100, $M^{+\bullet}$), 212 (55), 201 (11), 172 (10), 154 (88), 128 (27), 112 (68), 97 (33), 95 (18), 86 (16), 83 (22), 69 (26), 57 (24), 55 (17), 41 (34). Anal. Calcd for $C_{12}H_{22}N_2O_2S$: C, 55.78; H, 8.58; N, 10.84; S, 12.41%. Found: C, 55.69; H, 8.69; N, 10.77; S, 12.44%.

4.2.30. *trans* 4-(1-Methyl-1-nitroethyl)-6-phenylpiperidine-2-thione (**7k**)

White solid (122 mg, 44%), mp 194–197 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3456 br, 3148, 3052, 2988, 2936, 1536, 1452, 1400, 1348, 1116, 848, 760, 704 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=1.49 (6H, s, 2×CH_3), 1.91 (1H, dm, *J* 13.3 Hz, $CH H_{eq}$-5), 1.98 (1H, ddd, *J* 13.3, 11.6, 5.6 Hz, $CH H_{ax}$-5), 2.38 (1H, ddt, *J* 12.1, ca. 11.6, ca. 4.6 Hz, CH_{ax}-4), 2.67 (1H, dd, *J* 18.1, 12.0 Hz, $CH H_{ax}$-3), 3.19 (1H, ddd, *J* 18.1, 4.7, 2.1 Hz, $CH H_{eq}$-3), 4.86 (1H, dt, *J* 5.6, 3.4 Hz, CH_{eq}-6), 7.18 (2H, dm, *J* 7.3 Hz, C_6H_5), 7.34 (1H, tt, *J* ca. 7.2, ca. 1.3 Hz, C_6H_5), 7.39–7.43 (2H, m, C_6H_5), 8.74 (1H, s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.1, 23.9 (2×CH_3), 30.6 (CH_2-5), 35.8 (CH-4), 40.8 (CH_2-3), 57.6 (CH-6), 89.7 (CNO_2), 125.9, 128.4, 129.1, 139.7 (C_6H_5), 201.8 (C-2); GC–MS (EI, 70 eV): *m*/*z*=278 (100, $M^{+\bullet}$), 232 (44), 198 (29), 189 (16), 188 (16), 175 (57), 157 (50), 131 (13), 129 (30), 117 (39), 115 (21), 106 (50), 104 (34), 91 (70), 79 (17), 77 (27), 69 (49), 41 (26). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.06; S, 11.52%. Found: C, 60.46; H, 6.55; N, 10.09; S, 11.44%.

*4.2.31. trans 6-sec-Butyl-4-(1-methyl-1-nitroethyl)piperidine-2-thione (**7l**)*

Mixture of diastereomers. White solid (186 mg, 72%), mp 98–100 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3172, 3064, 2964, 1568, 1536, 1464, 1400, 1376, 1344, 1112, 852 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.88 and 0.89 (6H, two d, *J* 6.8 Hz, 2×C*H*$_3$CH), 0.91 and 0.94 (6H, two t, *J* 7.3 Hz, 2×CH$_2$C*H*$_3$), 1.06–1.30 (2H, m, 2×C*H*H), 1.39–1.80 (20H, 2×CH*H*, 2×C*H*CH$_3$, 4×CH$_3$, 2×CH$_2$-5), 2.48–2.66 (4H, m, 2×C*H*H-3, CH-4), 3.12 (2H, dm, *J* ca. 14.6 Hz, 2×CH*H*-3), 3.29–3.37 (2H, m, 2×CH-6), 8.77 and 8.67 (2H, two br s, 2×NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=11.0 and 11.1 (2×CH$_2$C*H*$_3$), 14.9 and 15.4 (2×CHC*H*$_3$), 21.0 and 21.1 (2×CC*H*$_3$), 24.3 and 24.9 (2×CH$_2$), 25.4 and 25.7 (2×CH$_2$), 37.4 and 37.5 (2×CH-4), 38.6 and 38.8 (2×C*H*CH$_3$), 40.8 and 40.8 (2×CH$_2$-3), 58.1 and 58.3 (2×CH-6), 90.3 and 90.4 (2×CNO$_2$), 200.9 and 201.0 (2×C-2); GC–MS (EI, 70 eV): *m*/*z*=258 (100, M$^{+\bullet}$), 212 (58), 201 (11), 182 (10), 154 (78), 128 (10), 112 (58), 97 (19), 83 (21), 69 (23), 41 (22). Anal. Calcd for $C_{12}H_{22}N_2O_2S$: C, 55.78; H, 8.58; N, 10.84; S, 12.41%. Found: C, 55.72; H, 8.70; N, 10.86; S, 12.45%.

*4.2.32. trans 6-Ethyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**7m**)*

White solid (205 mg, 76%), mp 144–146 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3172, 3064, 2936, 2868, 1564, 1530, 1452, 1352, 1124, 1106, 848, 828 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.96 (3H, t, *J* 7.3 Hz, CH$_3$), 1.15–1.43 (3H, m, 3×C*H*H), 1.46–1.80 (9H, m, 2×C*H*H, 3×CH*H*, 2×CH$_2$), 2.22 (1H, tt, *J* ca. 11.7, ca. 4.4 Hz, CH$_{ax}$-4), 2.45 (1H, br d, *J* ca. 13.5 Hz, CH*H*), 2.49 (1H, br d, *J* ca. 13.8 Hz, CH*H*), 2.63 (1H, dd, *J* 17.5, 12.2 Hz, CHH_{ax}-3), 3.18 (1H, br d, *J* 17.4 Hz, CHH_{eq}-3), 3.48 (1H, br s, CH$_{eq}$-6), 8.81 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=10.5 (CH$_3$), 22.1, 22.3, 24.6, 26.1 (4×CH$_2$), 28.3 br (CH$_2$-5), 30.6, 32.4 (2×CH$_2$), 37.9 br (CH-4), 40.2* (CH$_2$-3), 55.5 (CH-6), 93.4 (CNO$_2$), 198.8* (C-2); GC–MS (EI, 70 eV): *m*/*z*=270 (75, M$^{+\bullet}$), 224 (100), 190 (12), 142 (24), 116 (39), 81 (15), 67 (18), 58 (20), 55 (19), 41 (22). Anal. Calcd for $C_{13}H_{22}N_2O_2S$ requires: C, 57.75; H, 8.20; N, 10.36; S, 11.86%. Found: C, 57.72; H, 8.30; N, 10.36; S, 11.85%. *Signal visible at 230 K.

*4.2.33. trans 6-Butyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**7n**)*

White solid (227 mg 76%), mp 119–121 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3176, 3068, 2940, 2860, 1658, 1646, 1564, 1534, 1450, 1352, 1148, 1100, 844 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.91 (3H, t, *J* 7.0 Hz, CH$_3$), 1.16–1.49 (7H, m, 5×C*H*H, CH$_2$), 1.49–1.77 (9H, m, 2×C*H*H, 5×CH*H*, CH$_2$), 2.17–2.30 (1H, m, CH$_{ax}$-4), 2.46 (1H, br d, *J* ca. 14.3 Hz, CH*H*), 2.49 (1H, br d, *J* ca. 14.3 Hz, CH*H*), 2.60 (1H, dd, *J* 17.8, 11.8 Hz, CHH_{ax}-3), 3.15 (1H, ddd, *J* 17.8, 4.5, 1.9 Hz, CHH_{eq}-3), 3.45–3.56 (1H, m, CH$_{eq}$-6), 8.8 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH$_3$), 22.1, 22.2, 22.4, 24.6, 26.6, 28.0, 30.5, 32.4, 34.9 (9×CH$_2$), 37.5 (CH-4), 40.6 (CH$_2$-3), 54.2 (CH-6), 93.3 (CNO$_2$), 200.7 (C-2); GC–MS (EI, 70 eV): *m*/*z*=298 (39, M$^{+\bullet}$), 252 (100), 218 (20), 194 (13), 170 (30), 144 (19), 112 (17), 69 (16), 67 (18), 55 (17), 41 (22). Anal. Calcd for $C_{15}H_{26}N_2O_2S$: C, 60.37; H, 8.78; N, 9.39; S, 10.74%. Found: C, 60.35; H, 8.83; N, 9.36; S, 10.85%.

*4.2.34. trans 6-Hexyl-4-(1-nitrocyclohexyl)piperidine-2-thione (**7o**)*

White solid (261 mg, 80%), mp 75–76 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3164, 3060, 2944, 2864, 1572, 1540, 1450, 1344, 1102, 844 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.89 (3H, t, *J* 7.0 Hz, CH$_3$), 1.18–1.48 (12H, m, 4×C*H*H, 4×CH$_2$), 1.48–1.80 (8H, m, 2×C*H*H, 4×CH*H*, CH$_2$), 2.23 (1H, tt, *J* ca. 11.5, ca. 4.4 Hz, CH$_{ax}$-4), 2.45 (1H, br d, *J* ca. 14.5 Hz, CH*H*), 2.49 (1H, br d, *J* ca. 14.5 Hz, CH*H*), 2.61 (1H, dd, *J* 17.8, 11.7 Hz, CHH_{ax}-3), 3.16 (1H, dm, *J* 17.8 Hz, CHH_{eq}-3), 3.52 (1H, br s, CH$_{eq}$-6), 8.82 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=14.05 (CH$_3$), 22.1, 22.2, 22.5, 24.6, 25.9, 26.6, 28.9, 30.5, 31.6, 32.4, 35.3 (11×CH$_2$), 37.7 br (CH-4), 41.3 v br* (CH$_2$-3), 54.3 (CH-6), 93.3 (CNO$_2$), 200.2 v br* (C-2); GC–MS (EI, 70 eV): *m*/*z*=326 (<1, M$^{+\bullet}$), 279 (69), 264 (19), 246 (100), 208 (32), 194 (21), 184 (13), 151 (11), 128 (12), 117 (14), 91 (17), 79 (17), 67 (13), 55 (15), 41 (18). Anal. Calcd for $C_{17}H_{30}N_2O_2S$: C, 62.54; H, 9.26; N, 8.58; S, 9.82%. Found: C, 62.55; H, 9.33; N, 8.55; S, 9.93%. *Signal visible at 230 K.

*4.2.35. trans 6-Butyl-4-(1-nitroethyl)piperidine-2-thione (**7p** major)*

Configuration at C$_\alpha$NO$_2$ was not established. White solid, mp113–115 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3180 br, 3060, 2956, 1554, 1458, 1392, 1340, 1104, 812 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.92 (3H, t, *J* 6.8 Hz, CH$_2$C*H*$_3$), 1.25–1.39 (4H, m, 2×CH$_2$), 1.44–1.55 (1H, m, C*H*H), 1.59 (3H, d, *J* 6.7 Hz, CHC*H*$_3$), 1.56–1.74 (3H, m, CH$_2$-5, CH*H*), 2.38–2.51 (1H, m, CH$_{ax}$-4), 2.62 (1H, dd, *J* 18.2, 9.3 Hz, CHH_{ax}-3), 3.11 (1H, dd, *J* 18.2, 4.8 Hz, CHH_{eq}-3), 3.52–3.61 (1H, m, CH$_{eq}$-6), 4.45 (1H, dquintet, *J* 9.4, 6.7 Hz, CHNO$_2$), 8.76 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH$_2$C*H*$_3$), 17.2 (C*H*$_3$CH), 22.4, 27.7, 28.6 (3×CH$_2$), 33.8 (CH-4), 35.3 (CH$_2$-5), 41.1 (CH$_2$-3), 53.4 (CH-6), 86.0 (CHNO$_2$), 199.3 (C-2); GC–MS (EI, 70 eV): *m*/*z*=244 (57, M$^{+\bullet}$), 214 (11), 198 (30), 170 (20), 154 (22), 140 (19), 128 (11), 114 (21), 112 (100), 97 (23), 83 (22), 69 (30), 55 (39), 41 (29). Anal. Calcd for $C_{11}H_{20}N_2O_2S$: C, 54.07; H, 8.25; N, 11.46; S, 13.12%. Found: C, 54.15; H, 8.22; N, 11.50; S, 13.19%.

*4.2.36. trans 6-Butyl-4-(1-nitroethyl)piperidine-2-thione (**7p** minor)*

Configuration at C$_\alpha$NO$_2$ was not established. White solid, mp117–119 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3172, 3068, 2956, 2932, 1572, 1542, 1460, 1416, 1394, 1360, 1344, 1296, 1152, 1108 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.93 (3H, t, *J* 7.0 Hz, CH$_2$C*H*$_3$), 1.30–1.40 (4H, m, 2×CH$_2$), 1.45–1.60 (1H, m, C*H*H), 1.57 (3H, d, *J* 6.8 Hz, CHC*H*$_3$), 1.60–1.77 (2H, m, CH*H*, CHH_{ax}-5), 1.80 (1H, dm, *J* ca. 13.5, CHH_{eq}-5), 2.43–2.54 (1H, m, CH$_{ax}$-4), 2.64 (1H, dd, *J* 18.1, 10.2 Hz, CHH_{ax}-3), 3.08 (1H, ddd, *J* 18.1, 4.8, 1.5 Hz, CHH_{eq}-3), 3.48–3.57 (1H, m, CH$_{eq}$-6), 4.50 (1H, quintet, *J* 6.8 Hz, CHNO$_2$), 8.82 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH$_2$C*H*$_3$), 16.0 (C*H*$_3$CH), 22.4, 27.5, 27.9 (3×CH$_2$), 33.1 (CH-4), 35.2 (CH$_2$-5), 41.6 (CH$_2$-3), 53.6 (CH-6), 85.7 (CHNO$_2$), 199.8 (C-2); GC–MS (EI, 70 eV): *m*/*z*=244 (74, M$^{+\bullet}$), 214 (12), 198 (43), 170 (27), 154 (23), 140 (27), 128 (15), 112 (100), 97 (29), 83 (30), 69 (40), 55 (48), 41 (35); HRMS (EI) for $C_{11}H_{20}N_2O_2S$: calculated 244.1245, found 244.1242.

4.3. Synthesis of 4-nitroalkylpiperidine-2-ones (8)

Transformations of 4-nitroalkyl δ-thiolactams to the corresponding δ-lactams **8** were carried out according to the procedure described by Nowaczyk et al.[26] with some modification. To a solution of 4-nitroalkyl δ-thiolactam (**4f** or **5f** or **7b** or **7h**) (0.7 mmol) in acetone (10 ml) and water (1 ml), sodium bicarbonate (2.8 mmol) was added at 0–2 °C. To a stirred suspension oxone (0.35 mmol) was added. After 15 min of stirring the next 5 portions of oxone (0.175 mmol) were added at 15 min intervals. After addition of the last portion of oxone the solution was stirred for additional 30 min and water (10 ml) was added. (In the case of NH products **8f** and **8g** 5 ml of concentrated solution of NH_4Cl was also added.) The solution was extracted twice (2×50 ml) with ethyl acetate. The organic phase separated was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica and crystallized from the appropriate solvents.

*4.3.1. trans 6-Butyl-4-nitromethylpiperidin-2-one (**8f**)*

White solid (139 mg, 93%), mp 69–72 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3196 br, 2960, 2936, 1656, 1648, 1554, 1456, 1432, 1410, 1372, 1356, 1340 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.91 (3H, t, *J* 7.0 Hz, CH$_3$), 1.25–1.40 (4H, m, 2×CH$_2$), 1.44–1.62 (2H, m, CH$_2$), 1.73–1.80 (2H, m, CH$_2$-5), 2.16 (1H, dd, *J* 17.3,

7.8 Hz, CHH_{ax}-3), 2.55 (1H, dd, *J* 17.3, 5.7 Hz, CHH_{eq}-3), 2.83–2.95 (1H, m, CH-4), 3.50 (1H, quintet, *J* ca. 6.0 Hz, CH-6), 4.37–4.41 (2H, m, CH_2NO_2), 6.56 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9 (CH_3), 22.4, 27.8 (2×CH_3), 28.9 (CH-4), 29.9 (CH_2-5), 34.4 br (CH_2-3), 36.4 (6-CH_2), 49.7 (CH-6), 78.7 (CH_2NO_2), 169.6 (C-2); GC–MS (EI, 70 eV): *m*/*z*=214 (<1, $M^{+\bullet}$), 184 (9), 157 (53), 125 (11), 110 (25), 96 (100), 68 (18), 55 (10), 41 (14). Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.07%. Found: C, 56.01; H, 8.42; N, 12.99%.

*4.3.2. trans 6-Butyl-4-(1-methyl-1-nitroethyl)piperidin-2-one (**8g**)*

White needles (163 mg, 96%), mp 116–118 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3276 br, 2960, 2872, 1666, 1620 br, 1536, 1480, 1400, 1378, 1348, 1144, 808 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.91 (3H, t, *J* 7.0 Hz, CH_3), 1.20–1.38 (4H, m, 2×CH_2), 1.40–1.65 (4H, m, 6-CH_2, CH_2-5), 1.56 (3H, s, CH_3), 1.57 (3H, s, CH_3), 2.10 (1H, dd, *J* 17.0, 12.4 Hz, CHH_{ax}-3), 2.40 (1H, ddd, *J* 17.0, ca. 4.7, 1.7 Hz, CHH_{eq}-3), 2.63–2.73 (1H, m, CH-4), 3.43–3.51 (1H, m, CH-6), 6.73 (1H, br s, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=13.9, 21.4 (2×CH_3), 22.4 (CH_2), 24.2 (CH_3), 27.8 (CH_2-5), 28.2 (CH_2), 33.2 (CH_2-3), 35.8 (6-CH_2), 36.9 (CH-4), 50.4 (CH-6), 90.3 (CNO_2), 170.6 (C-2); GC–MS (EI, 70 eV): *m*/*z*=242 (<1, $M^{+\bullet}$), 212 (5), 196 (22), 194 (17), 185 (32), 152 (9), 138 (100), 110 (11), 96 (52), 86 (18), 69 (21), 55 (16), 41 (24). Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56%. Found: C, 59.55; H, 9.12; N, 12.00%.

*4.3.3. trans 6-Allyl-1-benzyl-4-(1-methyl-1-nitroethyl)piperidin-2-one (**8h**)*

Colorless oil (206 mg, 93%). IR (thin film): ν=2936, 1640, 1536, 1452, 1346, 1110, 924, 732, 704 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.39 (1H, td, *J* 13.2, 5.3 Hz, CHH_{ax}-5), 1.53 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.75 (1H, dquartet, *J* 13.2, 2.0 Hz, CHH_{eq}-5), 2.17–2.27 (1H, m, 6-C*H*H), 2.26 (1H, dd, *J* 17.4, 12.2 Hz, CHH_{ax}-3), 2.52–2.59 (1H, m, 6-CH*H*), 2.58 (1H, ddd, *J* 17.2, 5.9, 2.1 Hz, CHH_{eq}-3), 2.80 (1H, tdd, *J* ca. 12.5, ca. 5.9, 2.0 Hz, CH_{ax}-4), 3.35–3.43 (1H, m, CH_{eq}-6), 3.98 (1H, d, *J* 15.0 Hz, NC*H*H), 5.08–5.15 (2H, m, =CH_2), 5.36 (1H, d, *J* 15.0 Hz, NCH*H*), 5.52–5.64 (1H, m, =CH), 7.21 (2H, d, *J* 7.2 Hz, C_6H_5), 7.25–7.37 (3H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=21.5, 23.8 (2×CH_3), 26.9 (CH_2-5), 33.4 (CH_2-3), 36.4 (6-CH_2), 36.5 (CH-4), 47.8 (NCH_2), 53.8 (CH-6), 90.2 (CNO_2), 119.1 (=CH_2), 127.5, 127.8, 128.7, 137.0 (C_6H_5), 133.5 (=CH), 168.1 (C-2); GC–MS (EI, 70 eV): *m*/*z*=316 (<1, $M^{+\bullet}$), 315 (2), 275 (41), 228 (31), 186 (15), 91 (100); HRMS (EI) for $C_{18}H_{24}N_2O_3$: calculated 316.1787, found 316.1788.

*4.3.4. trans 4-(1-Nitrocyclohexyl)-1-phenylpiperidin-2-one (**8i**)*

White solid (184 mg, 87%), mp 183–185 °C from *n*-hexane/ethyl acetate. IR (KBr pellet): ν=3072, 2940, 1650, 1592, 1526, 1496, 1476, 1432, 1416, 1348, 1308, 768, 696 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.15–1.45 (3H, m, 3×C*H*H), 1.54–1.80 (6H, m, 2×CHH_{ax}, 3×CH*H*, CHH_{ax}-5), 2.01 (1H, dm, *J* ca. 12.6 Hz, CHH_{eq}-5), 2.36 (1H, tdd, *J* ca. 12.2, 4.3, 2.9 Hz, CH_{ax}-4), 2.43 (1H, dd, *J* 16.3, 12.3 Hz, CHH_{ax}-3), 2.52 (1H, dm, *J* ca. 16.5 Hz, CHH_{eq}), 2.57 (1H, dm, *J* ca. 16.4 Hz, CHH_{eq}), 2.69 (1H, dm, *J* ca. 16.3 Hz, CHH_{eq}-3), 3.62–3.68 (2H, m, CH_2-6), 7.21 (2H, dm, *J* ca. 7.4 Hz, C_6H_5), 7.27 (1H, tt, *J* 7.6, 1.2 Hz, C_6H_5), 7.39 (2H, t, *J* 7.7 Hz, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.1, 22.2, 24.6 (3×CH_2), 24.7 (CH_2-5), 30.4, 32.2 (2×CH_2), 34.0 (CH_2-3), 42.2 (CH-4), 50.3 (CH_2-6), 93.5 (CNO_2), 126.0, 127.1, 129.3, 142.4 (C_6H_5), 168.2 (C-2); GC–MS (EI, 70 eV): *m*/*z*=302 ($M^{+\bullet}$, 73), 256 (86), 174 (14), 146 (18), 119 (23), 106 (100), 81 (19), 77 (26), 67 (18), 55 (22), 41 (16); HRMS (EI) for $C_{17}H_{22}N_2O_3$: calculated 302.1630, found 302.1632.

Acknowledgements

Financial support by the National Committee for Scientific Research (KBN, Grant No. 3 T09A 106 28) is gratefully acknowledged.

References and notes

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (c) Drauz, K.; Schäfer, M.; Schwarm, M. Formation of C–N Bonds by Conjugate Addition of *N*-Nucleophiles. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl; Georg Thieme: Stuttgart, 1995; Vol. E21e, pp 5588–5642; (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (e) Jha, S. C.; Joshi, N. N. *ARKIVOC* **2002**, *vii*, 167–196; (f) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891; (g) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366; (h) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (i) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701–1716; (j) Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188; (k) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, *9*, 1279–1300.
2. For selected examples see: (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341; (b) Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C.; Kleven, M. *J. Med. Chem.* **1999**, *42*, 1648–1660; (c) Webber, R. K.; Metz, S.; Moore, W. M.; Connor, J. R.; Currie, M. G.; Fok, K. F.; Hagen, T. J.; Hansen, D. W., Jr.; Jerome, G. M.; Manning, P. T.; Pitzele, B. S.; Toth, M. V.; Trivedi, M.; Zupec, M. E.; Tjoeng, F. S. *J. Med. Chem.* **1998**, *41*, 96–101; (d) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472.
3. (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidines. Structure, Preparation, Reactivity and Synthetic Application of Piperidines and its Derivatives*; Elsevier: Amsterdam, 1991; For selected reviews on piperidines see: (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1849; (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (d) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892; (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989; (f) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729; (g) Huang, P.-Q. *Synlett* **2006**, 1133–1149; (h) Stead, D.; Brien, P. O. *Tetrahedron* **2007**, *63*, 1885–1897.
4. Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Thomson, J. E.; Toms, S. M. *Org. Biomol. Chem.* **2007**, *5*, 1961–19691.
5. See for example: (a) Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799–801; (b) Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *19*, 3243–3246; (c) Garcia, E.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2006**, *71*, 6776–6784; (d) Amat, M.; Llor, N.; Checa, B.; Pérez, M.; Bosch, J. *Tetrahedron Lett.* **2007**, *48*, 6722–6725; (e) Oueslati, F.; Perrio, C.; Dupas, G.; Barré, L. *Org. Lett.* **2007**, *9*, 153–156.
6. Pineschi, M.; Moro, F. D.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244–1246.
7. Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657–660.
8. (a) Hagen, T. J. *Synlett* **1990**, 3–66; Muller, M.; Schoenfelder, A.; Didier, B.; Mann, A.; Wermuth, C.-G. *Chem. Commun.* **1999**, 683–684; (b) Herdeis, C.; Kaschinski, C.; Karla, R.; Lotter, H. *Tetrahedron: Asymmetry* **1996**, *7*, 867–884; (c) Coe, D.; Drysdale, M.; Philps, Ol.; West, R.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, *22*, 2459–2472; (d) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827; (e) Lerchner, A.; Carreira, E. M. *Chem.—Eur. J.* **2006**, *12*, 8208–8219.
9. See for example: (a) Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719–730; (b) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; PérezLlor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084; (c) Ecija, M.; Diez, A.; Rubiralta, M.; Casamitjana, N.; Kogan, M. J.; Giralt, E. *J. Org. Chem.* **2003**, *68*, 9541–9553; (d) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848; (e) Camerero, C.; González-Temprano, I.; Lete, E.; Sotomayor, N. *Synlett* **2007**, 1101–1105; (f) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923.
10. Tinarelli, A.; Paolucci, C. *J. Org. Chem.* **2006**, *71*, 6630–6633; (c) Herdeis, C.; Waibel, D. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 269–274.
11. (a) Tamaru, Y.; Harada, T.; Iwamoto, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1978**, *100*, 5221–5223; (b) Tamaru, Y.; Kagotani, M.; Yoshida, Z.-i. *Tetrahedron Lett.* **1981**, *22*, 3409–3412.
12. Tamaru, Y.; Harada, T.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1979**, *101*, 1316–1318.
13. Sośnicki, J. G.; Jagodziński, T. S.; Liebscher, J. *J. Heterocycl. Chem.* **1997**, *34*, 643–648.
14. Sośnicki, J. G.; Jagodziński, T. S.; Hansen, P. E. *Tetrahedron* **2001**, *57*, 8705–8718.
15. (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971; (b) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Palmieri, A. *Pure Appl. Chem.* **2006**, *78*, 1857–1866; (c) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099–12121.
16. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, NY, 2001.
17. (a) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991–1994; (b) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173–2176.
18. Chavan, A. P.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879–6882.
19. Morrissette, M. M.; Williams, P. D.; Wai, J. S.; Fisher, T.; Lyle, T. A. PCT Int. Appl WO 2005086700 A2, 2005.
20. (a) Sośnicki, J. G.; Liebscher, J. *Synlett* **1996**, 1117–1118; (b) Sośnicki, J. G. *Synlett* **2003**, 1673–1677.
21. Sośnicki, J. G.; Westerlich, S. *Tetrahedron Lett.* **2002**, *43*, 1325–1328.
22. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
23. (a) Sośnicki, J. G.; Hansen, P. E. *J. Mol. Struct.* **2004**, *700*, 91–103; (b) Sośnicki, J. G.; Langaard, M.; Hansen, P. E. *J. Org. Chem.* **2007**, *72*, 4108–4116 and references cited therein.

24. For example: Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627.
25. Sośnicki, J. G. *Tetrahedron* **2007**, *63*, 11862–11877.
26. Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2001**, *66*, 7841–7848.
27. PM3 calculations were performed using the HyperChem program (7.52 release).
28. Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, A. *Tetrahedron* **1980**, *36*, 2783–2792.
29. Sośnicki, J. G. *Tetrahedron Lett.* **2009**, *50*, 178–181.