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Study of Reactions between 1,2-Diaza-1,3-butadienes and *N,N'*-Diaryl- or *N,N'*-Dialkylthioureas

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Abstract: 1,2-Diaza-1,3-butadienes react with *N,N'*-diarylthioureas to give 2-(arylimino)-2,3-dihydrothiazole derivatives, whereas with *N,N'*-dialkylthioureas to afford 5,5-disubstituted 3-alkyl-2-(alkylimino)-thiazolidin-4-one derivatives. Under basic conditions, these last products surprisingly give rise to 2-thioxo-1,3,7-triazaspiro[4.4]non-8-en-4-one and 5-oxo-4-(4-substituted 5-oxo-2-thioxoimidazolidin-4-yl)-2,5-dihydro-1*H*-pyrazole derivatives. In acidic medium, 5,5-disubstituted 3-alkyl-2-(alkylimino)-thiazolidin-4-ones are converted into 2-(alkylimino)-1-thia-3,7-diazaspiro[4.4]non-8-en-4-ones. X-Ray crystal structures of two products were determined.

Keywords: 1,2-Diaza-1,3-butadienes, thioureas, hydrazones, addition reactions, heterocycles

INTRODUCTION

The electronic arrangement of 1,2-diaza-1,3-butadienes determines their great affinity towards regiospecific nucleophilic attack on the terminal carbon of the conjugated azo-ene system by a variety of carbon- and hetero-nucleophiles (oxygen, nitrogen, sulfur, phosphorus *etc.*) often bearing several other functional groups.[1] This property is significantly influenced by electron-rich or electron-poor groups on the terminal carbon and/or on nitrogen of the azo-ene system. Nucleophilic attack leads to α-substituted hydrazone derivatives by means of 1,4-conjugate addition (Michael-type) of these reagents to the heterodiene system with the formation of a carbon-carbon or carbon-heteroatom single bond. It is worth emphasising that this is the prelude to a variety of several different functionalizations. In fact, the hydrazone moiety can be considered a protected carbonyl function in view of the fact that numerous methods exist for the removal of the hydrazino protecting group with the regeneration of the parent carbonyl compounds.[2] Therefore, the ability of 1,2-diaza-1,3-butadienes to readily undergo nucleophilic attack represents a valuable alternative route for the functionalization of carbon α to the carbonyl group. According to the specific circumstances, this reaction can proceed in various ways, making these compounds powerful tools in organic chemistry. Such examples include: the olefination process producing carbon-carbon or carbon-heteroatom double bond (azines, heterodiene and heterotriene systems);[1,3] oxidation of methylene into keto group;[4] formation of osazones;[5] synthesis of hydrazinoyl chlorides;[1] closure of heterorings

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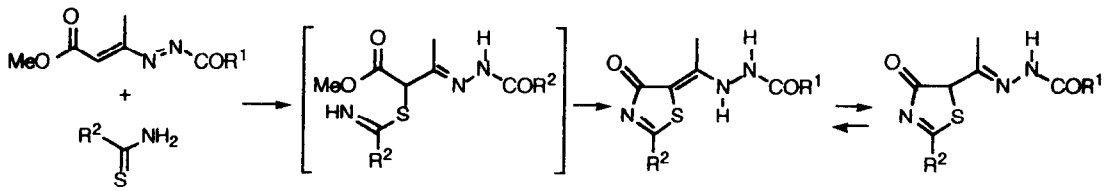
(pyrroles, pyrazoles, thiazoles, imidazoles, and pyridazines).[1,4,6,7] Other interesting syntheses and reactions of 1,2-diaza-1,3-butadienes have also been reported[8] and reviewed.[9,10]

We studied the reaction of 1,2-diaza-1,3-butadienes with thioamides or monosubstituted thioureas, which resulted in 5-hydrazino/hydrazono-2-thiazolin-4-one derivatives in tautomeric equilibrium (Scheme 1).[11]



Scheme 1. Reaction between 1,2-diaza-1,3-butadienes and thioamides, thiourea or monosubstituted thioureas.

As an ongoing part of our research into the synthesis of heterocyclic systems and more generally the overall synthetic usefulness of the conjugated azo-ene function, we now describe the different behaviour of 1,2-diaza-1,3-butadienes towards *N*,*N*'-diaryl- and *N*,*N*'-dialkyl-thioureas.

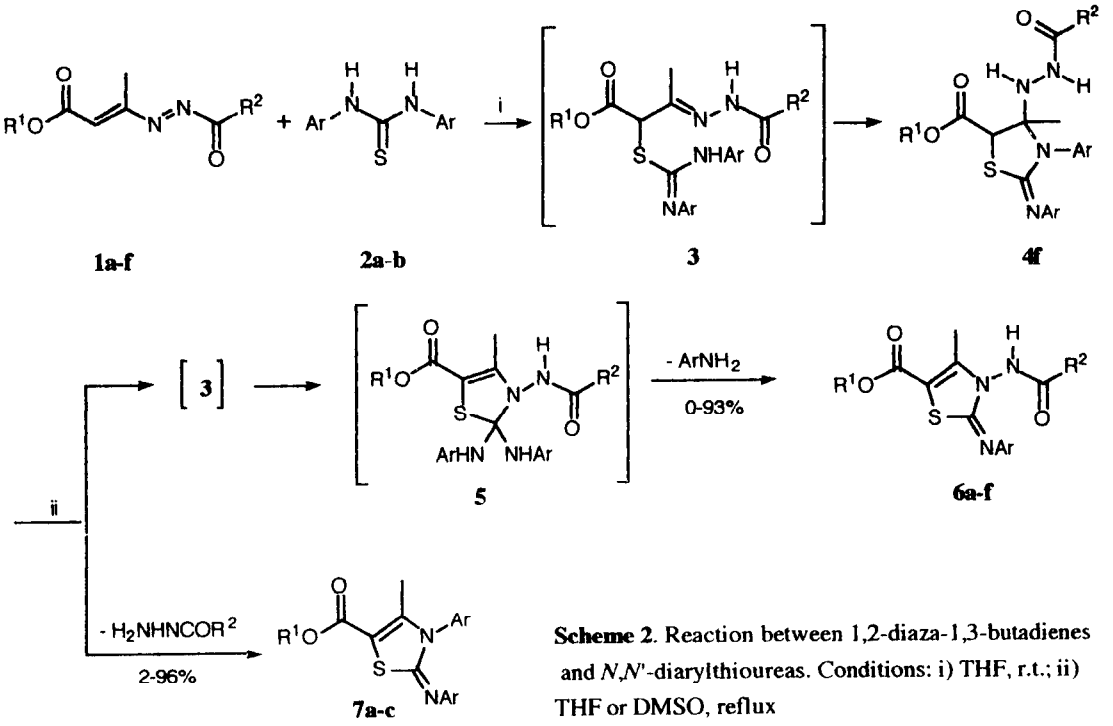
RESULTS AND DISCUSSION

Initially, we studied the reaction between 1,2-diaza-1,3-butadienes **1a-f** and *N*,*N*'-diphenylthiourea (**2a**). Using an equimolar ratio of substrates in MeOH, the reactions yielded complex mixtures with no obvious predominant product. Reactions between **1a-e** and **2a** were also carried out in THF, and also resulted in complex mixtures which degraded rapidly during any attempts at chromatographic separation. However, the reaction between **1f** and **2a** carried out in THF at room temperature yielded a precipitate, which was identified by ^{1}H- and ^{13}C-NMR as being the aminal **4f** (Scheme 2 and Table 1).

In accordance with our previous results,[11] we presume that the reaction proceeds *via* *S*-nucleophilic attack[12] on the terminal carbon of the heterodiene system to afford the hydrazone intermediate **3** by means of 1,4-conjugate addition (Michael-type). We assumed that thiazolidine **4f** is formed from **3** by a chain-ring tautomerism (Scheme 2). An in-depth analysis of the transformation products of **4f** was carried out. Evidence of tautomeric conversion into **3** and **5** (Scheme 2) was obtained by recording the variation with time of the resonances in ^{1}H-NMR spectra of **4f** in DMSO-d_6 . The spontaneous decrease of the signal at δ 1.16 ppm was observed, this signal is due to the methyl group on the sp^3 carbon of **4f**, and is accompanied by the contemporary appearance of two singlets: one at δ 1.75 ppm, which initially is more intense and is due to the methyl group of hydrazone **3**, and another at δ 2.18 ppm due to the methyl group on the sp^2 carbon of thiazoline **5**.

We therefore decided to carry out the reactions between **1a-f** and **2a** in THF at room temperature and then after the disappearance of the reagents under reflux in the same solvent. In the case of the reaction between **1f** and **2a**, the reflux was preferably carried out in DMSO to afford **6f** and **7b** within 0.4 h. These last derivatives were also obtained by refluxing in DMSO; **4f** was collected by filtration after the first step (78%). The choice of DMSO was due to the long reaction time observed at reflux in THF (up to 11 days). All these reactions produced 3-(carbonylamino)-2-(phenylimino)-2,3-dihydrothiazole derivatives **6a-f** in good to excellent yields (63-93%)

and 3-phenyl-2-(phenylimino)-2,3-dihydrothiazole derivatives **7a-b** as by-products (2-17%) (Scheme 2 and Table 1). At reflux temperature thiazolidine **4** transforms directly into compound **7** by loss of hydrazino residue, and into intermediate **3** by means of ring opening. Subsequent ring closure of the latter *via* the intramolecular nucleophilic attack of the hydrazone nitrogen atom on the thioimido group of the resulting 1,4-adduct could give rise to the intermediate **5**. In turn, this compound gives **6** with the loss of aniline.



Scheme 2. Reaction between 1,2-diaza-1,3-butadienes and *N,N'*-diarylthioureas. Conditions: i) THF, r.t.; ii) THF or DMSO, reflux

Table 1. Results of the reactions depicted in Scheme 2.

1	R^1	R^2	2	Ar	4	R^1	R^2	Ar	Yield[a] 4 [%]	6	R^1	R^2	Ar	Yield[a] 6 [%]	7	R^1	Ar	Yield[a] 7 [%]
a	Me	*t*-BuO	a	Ph						a	Me	*t*-BuO	Ph	78	a	Me	Ph	9
b	Me	MeO	b	*o*-Tol						b	Me	MeO	Ph	93	a	Me	Ph	3
c	Et	MeO								c	Et	MeO	Ph	78	b	Et	Ph	6
d	Et	BnO								d	Et	BnO	Ph	82	b	Et	Ph	2
e	Et	PhNH								e	Et	PhNH	Ph	63	b	Et	Ph	17
f	Et	NH_2			f	Et	NH_2	Ph	78	f	Et	NH_2	Ph	70	b	Et	Ph	8
c	Et	MeO													c	Et	*o*-Tol	96
e	Et	PhNH													c	Et	*o*-Tol	94

[a] Yield of pure isolated products.

On the contrary, the reaction between 1,2-diaza-1,3-butadienes **1c,e** and *N,N'*-di-*o*-tolylthiourea (**2b**) under the same conditions led exclusively to 3-*o*-tolyl-2-(*o*-tolylimino)-2,3-dihydrothiazole derivative **7c** in nearly quantitative yield (Scheme 2 and Table 1).

The 2,3-dihydrothiazole structure of compounds **6a-f** was unequivocally confirmed by X-ray diffraction study of **6b** (Figure1).

1,2-Diaza-1,3-butadienes participate in the thiazole ring assembly of **6a-f** with three membered N(3)-C(4)-C(5) part and *N,N'*-diphenylthiourea with two membered S(1)-C(2) group according to the Hantzsch reaction (type B),[13] in a different way from that previously observed.[11]

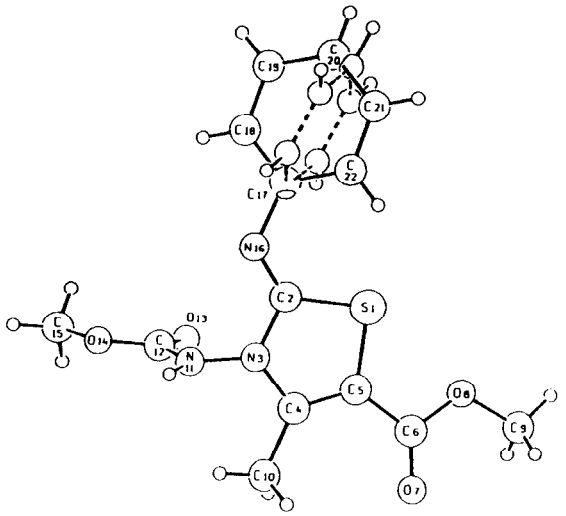
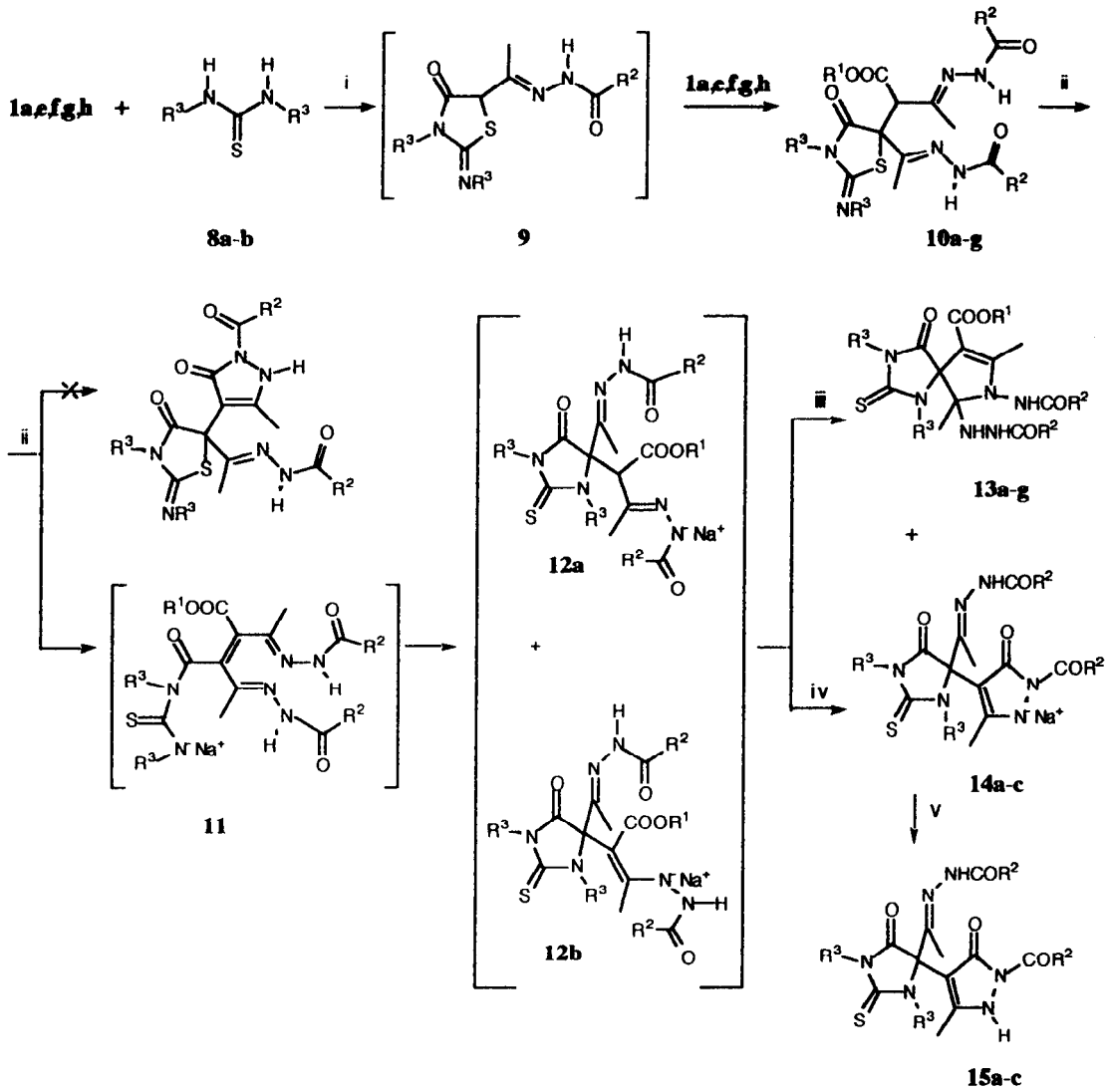


Figure 1. X-ray molecular structure of **6b** with the atom numbering system used in the crystallographic analysis.

The reaction in MeOH at room temperature between 1,2-diaza-1,3-butadienes **1a,e-h** and *N,N'*-dimethyl- (**8a**) or *N,N'*-diethyl-thiourea (**8b**) in equimolar ratio resulted in unreacted *N,N'*-dialkylthiourea despite the disappearance of 1,2-diaza-1,3-butadiene. Such behaviour suggested a different reaction pathway to that observed with *N,N'*-diarylthioureas. Carrying out the reactions between **1a,e-h** and **8a-b** in molar ratio of 2:1 in the same solvent, we observed the complete disappearance of both reagents and derivatives **10a-g** were obtained as diastereomeric mixtures. Spectroscopic data unequivocally demonstrated that these products were 5,5-disubstituted 3-alkyl-2-(alkylimino)-thiazolidin-4-ones **10a-g** (Scheme 3 and Table 2).

The experimental observations together with the spectral features suggest that these derivatives were formed according to the Hantzsch synthesis (type A)[13] through the intermediate **9**. While in previous investigations similar structures exhibited solely hydrazino-hydrazono tautomerism due to the hydrogen on the carbon in position 5 of the ring,[11] on this occasion that hydrogen is acidic enough to permit even in neutral conditions nucleophilic attack by the relevant carbanion on another conjugated azoalkene molecule giving rise to compounds **10**.

Under basic conditions, **10** could give rise to 4-(5-substituted 2-imino-4-oxothiazolidin-5-yl)-5-oxo-2,5-dihydro-1*H*-pyrazole derivatives by means of an heterocyclization process involving the hydrazone side chain bearing the ester group, in accordance with our previous results.[1,7] Unexpectedly, treatment of compounds **10a,d,f** with NaH led exclusively to **13a,d,f**, whereas when **10b,c,e,g** were subjected to the same treatment, a mixture resulted of **13b,c,e,g** and **14a-c** (Scheme 3 and Table 2).



Scheme 3. Reaction between 1,2-diaza-1,3-butadienes and *N,N'*-dialkylthioureas. Conditions: i) MeOH at r.t.; ii) 1 equiv NaH, MeOH or MeOH:THF 1:1; iii) organic layer at pH 7; iv) aqueous phase at pH 7; v) MeOH, TFA excess, 0 °C.

More conveniently, 2-thioxo-1,3,7-triazaspiro[4.4]non-8-en-4-one derivatives **13a-g** and 5-oxo-4-(4-substituted 5-oxo-2-thioxoimidazolidin-4-yl)-2,5-dihydro-1*H*-pyrazole derivatives **14a-c** can be directly obtained by a one-pot reaction, without isolation of the corresponding intermediates **10**. After an appropriate extractive work-up procedure, **14a-c** were separated from **13b,c,e,g**. Subsequent acidification of **14a-c** with

TFA (trifluoroacetic acid) in MeOH gave **15a-c** (Table 2). The ^{13}C-NMR spectra in DMSO-d_6 of compounds **13-15** showed a singlet at δ 180 ppm not present in the spectra of **10** and ascribable to the C=S function.

Table 2. Results of the reactions depicted in Scheme 3.

1	R^1	R^2	8	R^3	10	13	R^1	R^2	R^3	Yield[a] 13 [%]	14	15	R^2	R^3	Yield[a] 15 [%]
a	Me	*t*-BuO	a	Me	a	a	Me	*t*-BuO	Me	97					
e	Et	PhNH	a	Me	b	b	Et	PhNH	Me	56	a	a	PhNH	Me	36
f	Et	NH_2	a	Me	c	c	Et	NH_2	Me	44	b	b	NH_2	Me	28
g	Et	*t*-BuO	a	Me	d	d	Et	*t*-BuO	Me	71					
h	Me	NH_2	a	Me	e	e	Me	NH_2	Me	49	b	b	NH_2	Me	26
a	Me	*t*-BuO	b	Et	f	f	Me	*t*-BuO	Et	78					
h	Me	NH_2	b	Et	g	g	Me	NH_2	Et	43	c	c	NH_2	Et	20

[a] Yield of pure isolated products.

An X-ray diffraction study of **13d** confirmed the complex structure of **13**. The drawing clearly shows the pyrroline-imidazolidine spiro condensed ring on C(7), having S(1) exocyclic sulfur as well as N(3) and N(8) endocyclic nitrogens in the imidazolidine heterocycle (Figure 2).

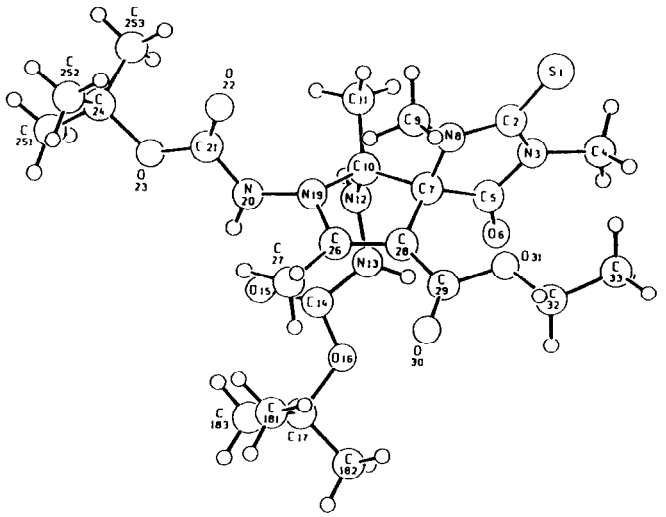


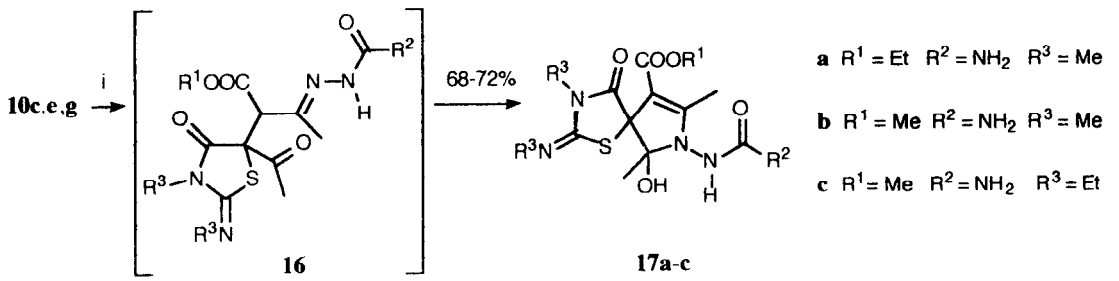
Figure 2. X-ray molecular structure of **13d** with the atom numbering system used in the crystallographic analysis

Two important observations were made in the base-promoted rearrangement of **10** to **13** and **14** that merit comment. The first of these is the formation of the imidazole ring. This would implicate endocyclic-exocyclic transformation for sulfur and *vice-versa* for nitrogen and this can be explained only in terms of a base-induced ring cleavage[14] of the thiazolidinone skeleton of **10** to give the intermediate **11**. Subsequent ring closure caused by nucleophilic attack of the thioureic negatively charged nitrogen on the olefinic moiety leads to 5,5-disubstituted 2-thioxoimidazolidin-4-one intermediates **12a-b**. The second observation is the formation of a new pyrrole or

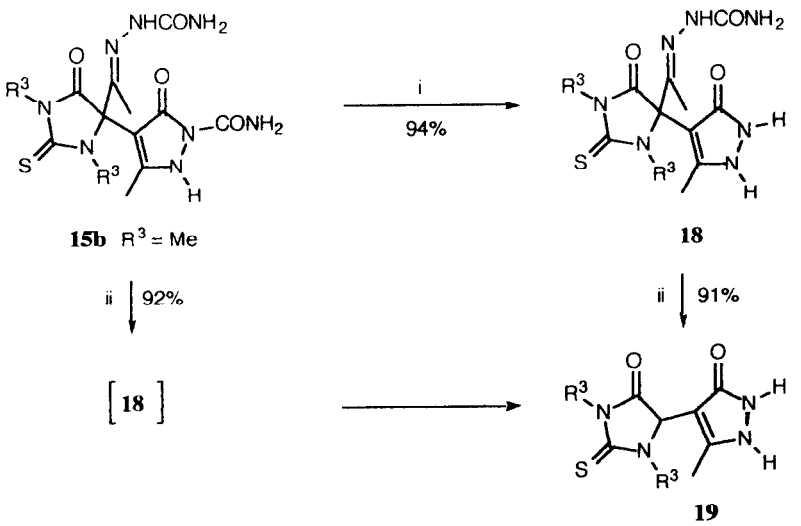
pyrazole ring, either of which can be formed from **12a-b**. To afford **13** the two hydrazone side chains partake in the pyrrole ring closure producing spiro condensed heterocyclic systems, while in compound **14** only the hydrazone side chain bearing the ester function generates the pyrazole ring closure (Scheme 3).

In acidic medium, the thiazolidinonic nucleus of compounds **10c,e,g** was preserved affording 2-(alkylimino)-1-thia-3,7-diazaspiro[4.4]non-8-en-4-one derivatives **17a-c** (Scheme 4). It is probable that under these conditions cleavage of the hydrazone function at position 5 of the thiazolidinone ring generates a carbonyl group in the intermediate **16**. Subsequent nucleophilic attack by the hydrazone nitrogen atom at that carbonyl function produces an intramolecular heterocyclization process, with the formation of a spiro condensed pyrroline **17**, in agreement with our previous findings.[1] ^{13}C-NMR in DMSO-d_6 of compounds **17a-c** indicated the absence of a C=S group. NOE experiments were performed on compound **17b** to confirm its structure.

Under solvolytic conditions (Scheme 5), compound **15b** produced the *N*-unsubstituted pyrazole derivative



Scheme 4. Synthesis of compounds **17a-c**. Conditions: i) TFA excess, THF:H_2O 1:1, reflux.

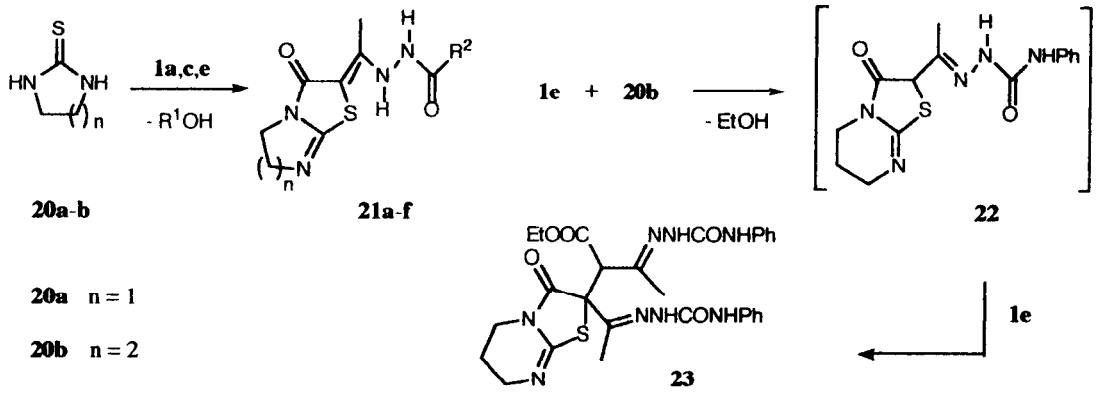


Scheme 5. Synthesis of compounds **18** and **19**. Conditions: i) MeOH, reflux; ii) TFA excess, THF:H_2O 1:1, reflux.

18 by loss of the $CONH_2$ group, according to our previous analogous findings.[1,7] Reaction of **15b** with TFA in THF/H_2O mixture at reflux unexpectedly gave compound **19**, *via* the intermediate **18**. This reaction pathway was confirmed by TLC analysis and direct treatment of compound **18** with the same hydrolytic conditions (Scheme 5).

Finally, we studied the reaction between 1,2-diaza-1,3-butadienes **1a,c,e** and cycloalkylthioureas **20a-b** (Scheme 6 and Table 3) in equimolar ratio in MeOH at room temperature: under these conditions, we observed total disappearance of **1a,c,e** and unreacted **20a-b** as for *N,N'*-dialkylthioureas. Although the reactions gave complicated mixtures, it was possible to isolate **21b,c,f** by filtration of the precipitates formed. Compounds **21a,d,e** were obtained by recrystallization from the crude products using appropriate solvents. Chromatographic purification of the mother liquors of compound **21f** allowed us to isolate **23**. When **1e** and **20b** reacted in 2:1 molar ratio, they produced 2-(1-substituted ethylidene)-6,7-dihydro-5*H*-thiazole[3,2-*a*]pyrimidin-3(2*H*)-one derivative **21f** as minor product and 2,2-disubstituted 6,7-dihydro-5*H*-thiazole[3,2-*a*]pyrimidin-3(2*H*)-one derivative **23** as major product (Scheme 6 and Table 3).

These results appeared quite similar to those of *N,N'*-dialkylthioureas (Scheme 3). However, any attempt to transform **23** under basic or hydrolytic conditions failed, likely owing to the greater stability of thiazolo[3,2-*a*]pyrimidine skeleton which hinders the ring opening and the subsequent rearrangement observed for *N,N'*-dialkylthioureas.



Scheme 6. Reaction between 1,2-diaza-1,3-butadienes and cycloalkylthioureas.

CONCLUSION

The diversity of reactions between 1,2-diaza-1,3-butadienes and some *N,N'*-diaryl- or *N,N'*-dialkyl-thioureas was studied. Interesting evidence regarding the different pathways of these reactions was reported and discussed in detail, as well as some conversions of the reaction intermediates and/or products were examined closely. By means of these investigations, 1,2-diaza-1,3-butadienes were confirmed to be fascinating tools in organic chemistry as efficient electrophilic substrates towards thioureic reagents. The Hantzsch cyclization behaviour of some adduct intermediates as well as the "anti-Hantzsch" annulation of some cyclic derivatives

Table 3. Results of the reactions depicted in Scheme 6.

1	R^1	R^2	20	n	21	n	R^2	Molar Ratio 1:20	Yield[a] 21 [%]	Yield[a] 23 [%]
a	MeO	*t*-BuO	**a**	1	**a**	1	*t*-BuO	1:1	62	
c	EtO	MeO	**b**	2	**b**	1	MeO	1:1	36	
e	EtO	PhNH			**c**	1	PhNH	1:1	27	
					d	2	*t*-BuO	1:1	75	
					e	2	MeO	1:1	34	
					f	2	PhNH	1:1	45	22
					f	2	PhNH	2:1	6	84

[a] Yield of pure isolated products.

owing to ring-opening and ring-closing process were also discussed. These reactions represent a useful entry to complex heterocyclic structures not easily synthesizable by other procedures: *i*) substituted 2,3-dihydrothiazoles; *ii*) polyfunctionalized thiazolidin-4-ones in turn yielding spiro imidazolidine or thiazolidine compounds or even imidazolidinyl-pyrazole systems; *iii*) condensed imidazo-thiazole or thiazole-pyrimidine derivatives.[15] On the other hand, these rings are very important as they are the central feature of a number of valuable organic, polymeric, natural, medicinal[16] and agricultural products.[17]

EXPERIMENTAL SECTION

General. 1,2-Diaza-1,3-butadienes **1a-h** were synthesized as standard isomeric mixtures according to previously reported procedures.[18,19] Starting materials for the preparation of the above-mentioned reagents as well as *N,N'*-diphenylthiourea (**2a**), *N,N'*-di-*o*-tolylthiourea (**2b**), *N,N'*-dimethylthiourea (**8a**), *N,N'*-diethylthiourea (**8b**), 2-imidazolidinethione (**20a**), 3,4,5,6-tetrahydro-2-pyrimidinethiol (**20b**), sodium hydride and solvents were purchased and used without further purification with the exception of THF which was distilled from sodium hydroxide. Melting points were determined in open capillary tubes and are uncorrected. IR-FT spectra were obtained as Nujol mulls. Mass spectra were made at an ionizing voltage of 70 eV. ^{1}H-NMR spectra were recorded at 200 MHz in DMSO-d_6 and ^{13}C-NMR at 50.32 MHz in the same solvent. Chemical shifts (δ) are reported relative to TMS as internal standard. All coupling constants (J) refer to ^3J(H,H). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; all the NH and OH exchanged with D_2O. NOE enhancement factors were determined on degassed DMSO-d_6 0.01 M solutions at 300 K, using NOEDIFF pulse program. Generally, irradiation time was 2 sec, with a power level of 31 low. Dynamic ^{1}H-NMR experiments were performed in DMSO-d_6 between 293-353 K. Diastereomeric ratios (d.r.) of compounds **10a-g** and **23** (unassigned configurations) were obtained from ^{1}H-NMR spectra in DMSO-d_6; the NMR data of the major diastereomer are marked *. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35-70 μ for column chromatography.

Preparation of 3-substituted 5-(alkoxycarbonyl)-2-(arylimino)-4-methyl-2,3-dihydrothiazoles[20] **(6a-f) and (7a-b).** 1,2-Diaza-1,3-butadienes **1a-e** (1 mmol) and **2a** (1 mmol) dissolved in THF (10 mL) were magnetically stirred at room temperature until their disappearance (0.6-1.0 h, checked by TLC). The reaction mixture was then refluxed in the same solvent until a TLC check revealed the presence of **6a-e** as major components, **7a-b** as by-product and aniline (identified by comparison with an authentic sample) (3-7 h). After removal of the solvent *in vacuo*, the residue was dissolved in EtOAc, washed with brine and 2N HCl to remove aniline. The crude reaction mixture was neutralized, dried over Na_2SO_4, evaporated *in vacuo*, and purified by flash-chromatography on a silica-gel column (eluent, cyclohexane-EtOAc mixtures). In the case of **1f** (1 mmol) and **2a** (1 mmol) dissolved in THF (10 mL), a solid precipitate (**4f**) was formed during the reaction. After the total disappearance of both reagents (1 h), THF was removed *in vacuo* and the crude product was refluxed in DMSO (20 mL) until a TLC check revealed the presence of **6f** as major component and **7b** (0.4 h). The work-up procedure was performed as above.

4f: ^{1}H-NMR: δ 7.46-7.35 (m, 6H, NH and 5H aromatic), 7.24 (t, *J* = 7.5 Hz, 2H, aromatic), 6.98 (t, *J* = 7.1 Hz, 1H, aromatic), 6.80 (d, *J* = 7.6 Hz, 2H, aromatic), 5.92 (br s, 2H, NH_2), 5.69 (s, 1H, NH), 4.60 (s, 1H, CH), 4.18 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.16 (s, 3H, CH_3); ^{13}C-NMR: δ 169.7, 160.5, 157.0, 151.0, 138.8, 130.2, 128.8, 128.7, 127.5, 122.9, 121.5, 82.5, 61.4, 51.6, 19.6, 13.9; IR: ν_{max} 3381, 3287, 3188, 3080, 1743, 1700, 1634, 1589 cm^{-1}. Anal. Calcd for $C_{20}H_{23}N_5O_2S$ (397.5): C, 60.43; H, 5.83; N, 17.62. Found: C, 60.54; H, 5.71; N, 17.41.

6a: 78% yield; mp 119-122 °C from THF/*n*-pentane; ^{1}H-NMR: δ 10.18 and 9.77 (2s, 1H, NH), 7.37 (t, *J* = 7.7 Hz, 2H, aromatic), 7.08 (t, *J* = 7.3 Hz, 1H, aromatic), 6.96 (d, *J* = 7.4 Hz, 2H, aromatic), 3.72 (s, 3H, OCH_3), 2.41 and 2.38 (2s, 3H, CH_3), 1.48 and 1.37 (2s, 9H, OBu^t); ^{13}C-NMR: δ 161.4, 154.6 and 154.1, 153.6, 149.6 and 149.2, 148.0 and 147.8, 129.7 and 129.6, 123.8, 120.7 and 120.6, 95.4, 81.3 and 80.9, 52.1, 27.9 and 27.7, 12.4 and 12.3; IR: ν_{max} 3304, 1734, 1714, 1633, 1611, 1594 cm^{-1}; MS: *m/z* (%) 363 (17) [M$^+$], 307 (7), 263 (100); Anal. Calcd for $C_{17}H_{21}N_3O_4S$ (363.4): C, 56.18; H, 5.82; N, 11.57. Found: C, 56.32; H, 5.53; N, 11.80.

6b: 93% yield; mp 123-126 °C from THF/*n*-pentane; ^{1}H-NMR: δ 10.56 and 10.11 (2s, 1H, NH), 7.37 (t, *J* = 7.7 Hz, 2H, aromatic), 7.09 (t, *J* = 7.3 Hz, 1H, aromatic), 6.97 (d, *J* = 7.5 Hz, 2H, aromatic), 3.72 (s, 3H, $COOCH_3$), 3.74 and 3.69 (2s, 3H, $NCOOCH_3$), 2.39 (s, 3H, CH_3); ^{13}C-NMR: δ 161.3, 156.0 and 155.6, 153.8, 149.3, 147.8 and 147.6, 129.6, 123.8, 120.7, 95.8, 53.0, 52.1, 12.2; IR: ν_{max} 3229, 1717, 1630, 1614, 1590, 1573 cm^{-1}; MS: *m/z* (%) 321 (100) [M$^+$], 289 (27), 247 (27). Anal. Calcd for $C_{14}H_{15}N_3O_4S$ (321.4): C, 52.33; H, 4.70; N, 13.08. Found: C, 52.10; H, 4.85; N, 13.29.

6c: 78% yield; mp 120-123 °C from CH_2Cl_2-Et_2O; ^{1}H-NMR: δ 10.57 and 10.12 (2s, 1H, NH), 7.37 (t, *J* = 7.7 Hz, 2H, aromatic), 7.09 (t, *J* = 7.3 Hz, 1H, aromatic), 6.95 (d, *J* = 7.4 Hz, 2H, aromatic), 4.18 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.74 and 3.68 (2s, 3H, $NCOOCH_3$), 2.39 (s, 3H, CH_3), 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 161.0, 156.0 and 155.7, 154.0, 149.4, 147.7 and 147.4, 129.6, 123.8, 120.7, 96.1, 60.8, 53.0, 14.1, 12.2; IR: ν_{max} 3274, 1720, 1698, 1643, 1608, 1593 cm^{-1}; MS: *m/z* (%) 335 (100) [M$^+$], 303

(28), 290 (6). Anal. Calcd for $C_{15}H_{17}N_3O_4S$ (335.4): C, 53.72; H, 5.11; N, 12.53. Found: C, 53.84; H, 5.21; N, 12.60.

6d: 82% yield; mp 99-102 °C from Et_2O-petroleum ether (40-60 °C); ^{1}H-NMR: δ 10.69 and 10.26 (2s, 1H, NH), 7.42-7.30 (m, 7H, aromatic), 7.10 (t, J = 7.2 Hz, 1H, aromatic), 6.97-6.86 (m, 2H, aromatic), 5.34-5.09 (m, 2H, OCH_2Ph), 4.19 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 2.40 (s, 3H, CH_3), 1.22 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 160.9, 156.0 and 155.0, 153.7, 149.2, 147.6 and 147.3, 136.0, 129.6, 128.4, 128.2, 127.9, 127.3, 123.8, 120.7, 96.1, 67.0 and 66.7, 60.9, 14.1, 12.2; IR: ν_{max} 3130, 1740, 1716, 1623, 1590 cm^{-1}; MS: m/z (%) 411 (10) [M$^+$], 335 (10), 277 (10), 135 (100). Anal. Calcd for $C_{21}H_{21}N_3O_4S$ (411.5): C, 61.30; H, 5.14; N, 10.21. Found: C, 61.49; H, 5.32; N, 10.39.

6e: 63% yield; mp 162-165 °C from MeOH-Et_2O; ^{1}H-NMR: δ 9.49 (s, 1H, NH), 9.15 (s, 1H, NH), 7.52-7.25 (m, 6H, aromatic), 7.08-6.94 (m, 4H, aromatic), 4.20 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 2.44 (s, 3H, CH_3), 1.23 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 161.1, 154.7, 154.0, 149.6, 148.8, 138.8, 129.7, 128.9, 123.8, 122.7, 120.8, 118.7, 95.6, 60.8, 14.2, 12.6; IR: ν_{max} 3308, 3151, 1705, 1678, 1628, 1592, 1563 cm^{-1}; MS: m/z (%) 396 (0.5) [M$^+$], 303 (100), 262 (34), 233 (72). Anal. Calcd for $C_{20}H_{20}N_4O_3S$ (396.5): C, 60.59; H, 5.08; N, 14.13. Found: C, 60.44; H, 5.35; N, 14.00.

6f: 70% yield; mp 172-175 °C from EtOAc-Et_2O; ^{1}H-NMR: δ 8.93 (br s, 1H, NH), 7.36 (t, J = 7.6 Hz, 2H, aromatic), 7.08 (t, J = 7.9 Hz, 1H, aromatic), 6.95 (d, J = 8.0 Hz, 2H, aromatic), 6.50 (s, 2H, NH_2), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.38 (s, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 161.1, 157.2, 154.8, 149.8, 149.0, 129.6, 123.6, 120.7, 95.3, 60.6, 14.2, 12.5; IR: ν_{max} 3418, 3271, 3195, 1708, 1675, 1634, 1591 cm^{-1}; MS: m/z (%) 320 (21) [M$^+$], 303 (100), 277 (84). Anal. Calcd for $C_{14}H_{16}N_4O_3S$ (320.4): calcd C, 52.49; H, 5.03; N, 17.49. Found: C, 52.25; H, 5.19; N, 17.25.

7a: 3-9% yield; mp 109-113 °C from Et_2O-petroleum ether (40-60 °C); ^{1}H-NMR: δ 7.61-7.46 (m, 5H, aromatic), 7.29 (t, J = 7.7 Hz, 2H, aromatic), 7.02 (t, J = 7.3 Hz, 1H, aromatic), 6.87 (d, J = 7.4 Hz, 2H, aromatic), 3.69 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3); ^{13}C-NMR: δ 161.6, 157.1, 150.5, 147.5, 136.3, 129.6, 129.5, 129.2, 129.0, 123.5, 120.6, 98.7, 51.9, 14.2; IR: ν_{max} 1704, 1612, 1578 cm^{-1}; MS: m/z (%) 324 (100) [M$^+$], 293 (2), 265 (2). Anal. Calcd for $C_{18}H_{16}N_2O_2S$ (324.4): C, 66.65; H, 4.97; N, 8.64. Found: C, 66.43; H, 4.72; N, 8.76.

7b: 2-17% yield; mp 150-153 °C from THF/*n*-pentane; ^{1}H-NMR: δ 7.60-7.49 (m, 5H, aromatic), 7.32 (t, J = 8.1 Hz, 2H, aromatic), 7.04 (t, J = 8.0 Hz, 1H, aromatic), 6.89 (d, J = 8.1 Hz, 2H, aromatic), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.21 (s, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 161.2, 157.2, 150.5, 147.3, 136.3, 129.6, 129.5, 129.1, 129.0, 123.4, 120.6, 98.9, 60.5, 14.1; IR: ν_{max} 1696, 1614, 1586 cm^{-1}; MS: m/z (%) 338 (100) [M$^+$], 309 (43), 293 (3). Anal. Calcd for $C_{19}H_{18}N_2O_2S$ (338.4): C, 67.43; H, 5.36; N, 8.28. Found: C, 67.25; H, 5.42; N, 8.46.

Preparation of 5-(ethoxycarbonyl)-4-methyl-3-*o*-tolyl-2-(*o*-tolylimino)-2,3-dihydrothiazole (7c). 1,2-Diaza-1,3-butadienes **1c,e** (1 mmol) and **2b** (1 mmol) were dissolved in THF (10 mL) and stirred at room temperature until their disappearance (monitored by TLC, 15-30 min). The crude reaction mixture was then refluxed until a TLC check revealed **7c** as major product (5-8.5 h). After removal of the solvent *in vacuo*, the residue was purified by chromatography on a silica-gel column (cyclohexane-EtOAc mixtures) to yield **7c**. 94-96% yield; oil; ^{1}H-NMR: δ 7.49-7.40 (m, 4H, aromatic), 7.15 (t, *J* = 8.2 Hz, 2H, aromatic), 6.95 (t, *J* = 7.4 Hz, 1H, aromatic), 6.80 (d, *J* = 7.2 Hz, 1H, aromatic), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.21 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.20 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 161.1, 155.6, 149.2, 146.9, 136.3, 135.4, 131.0, 130.6, 129.5, 129.0, 127.3, 126.9, 123.4, 119.2, 99.2, 60.4, 17.0, 16.8, 14.1, 13.6; IR: ν_{max} 1706, 1623, 1593, 1575 cm^{-1}; MS: *m/z* (%) 366 (100) [M$^+$], 351 (48), 323 (12), 260 (47). Anal. Calcd for $C_{21}H_{22}N_2O_2S$ (366.5): C, 68.83; H, 6.05; N, 7.64. Found: C, 68.94; H, 6.17; N, 7.79.

Preparation of 5,5-disubstituted 3-alkyl-2-(alkylimino)-thiazolidin-4-one derivatives[20] (10a-g). 1,2-Diaza-1,3-butadienes **1a,e-h** (2 mmol) and **8a-b** (1 mmol) were dissolved in MeOH (20 mL) at room temperature. The red solution changed colour to pale yellow when both reagents disappeared (0.5 h). The solid products formed during the reaction (**10b,c,e,g**) were filtered off. In those cases when the reaction did not directly give the precipitate, after removal of MeOH *in vacuo*, **10a,d,f** were recrystallized from appropriate solvents. Derivatives **10a-g** were obtained as diastereomeric mixtures.

10a: 65% yield; d.r. 27:73; white solid from EtOAc/*n*-pentane-Et_2O; ^{1}H-NMR: δ 9.83 and 9.76* (2s, 1H, NH), 9.60 and 9.53* (2s, 1H, NH), 4.51* and 4.33 (2s, 1H, CH), 3.63 and 3.59* (2s, 3H, OCH_3), 3.09*, 3.07, 3.05* and 3.02 (4s, 6H, $2NCH_3$), 2.10*, 1.75 and 1.72* (3s, 6H, $2CH_3$), 1.46*, 1.44* and 1.42 (3s, 18H, $2OBu^t$); IR: ν_{max} 3319, 3235, 3140, 1746, 1729, 1715, 1637, 1511 cm^{-1}; MS: *m/z* (%) 528 (6) [M$^+$], 397 (12), 341 (45), 297 (98), 284 (100). Anal. Calcd for $C_{22}H_{36}N_6O_7S$ (528.6): C, 49.99; H, 6.86; N, 15.90. Found: C, 50.13; H, 6.71; N, 15.73.

10b: 97% yield; d.r. 46:54; white solid from MeOH; ^{1}H-NMR: δ 10.05 and 10.03 (2s, 1H, NH), 9.83* and 9.78* (2s, 1H, NH), 8.63*, 8.49, 8.31 and 8.16* (4s, 2H, 2NH), 7.66-6.99 (m, 10H, aromatic), 5.52* and 5.10 (2s, 1H, CH), 4.27-3.86 (m, 2H, OCH_2CH_3), 3.19*, 3.14*, 3.08 and 3.01 (4s, 6H, $2NCH_3$), 2.14, 1.91*, 1.88 and 1.87* (4s, 6H, $2CH_3$), 1.16-1.03 (m, 3H, OCH_2CH_3); IR: ν_{max} 3386, 3367, 3198, 3093, 3066, 1721, 1692, 1658, 1596, 1536 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_8O_5S$ (580.7): C, 55.85; H, 5.55; N, 19.30. Found: C, 55.73; H, 5.37; N, 19.42.

10c: 98% yield; d.r. 38:62; white solid from MeOH; ^{1}H-NMR: δ 9.55*, 9.37*, 9.32 and 9.28 (4s, 2H, 2NH), 6.30 and 6.17* (2br s, 4H, $CONH_2$), 5.11 and 4.50* (2s, 1H, CH), 4.23-3.90 (m, 2H, OCH_2CH_3), 3.10*, 3.09, 3.06 and 3.03* (4s, 6H, $2NCH_3$), 1.97, 1.80*, 1.78 and 1.75* (4s, 6H, $2CH_3$), 1.21-1.05 (m, 3H, OCH_2CH_3); ^{13}C-NMR: δ 171.9 and 171.3, 169.7 and 168.9, 156.9 and 156.8, 153.1 and 152.8, 144.6 and 142.1, 142.0 and 140.9, 66.5 and 65.5, 61.3 and 61.2, 56.0 and 55.4, 37.9 and 37.6, 29.3 and 29.2, 18.1 and 16.4, 13.7, 13.0 and 13.2; IR: ν_{max} 3470, 3446, 3304, 3200, 1731, 1715, 1696, 1674, 1646, 1593 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_8O_5S$ (428.5): C, 42.05; H, 5.65; N, 26.15. Found: C, 42.21; H, 5.43; N, 26.32.

10d: 63% yield; d.r. 25:75; white solid from EtOAc/*n*-pentane-Et_2O; ^{1}H-NMR: δ 9.83 and 9.76* (2s, 1H, NH), 9.59 and 9.54* (2s, 1H, NH), 4.50* and 4.34 (2s, 1H, CH), 4.13-3.94 (m, 2H, OCH_2CH_3), 3.08*, 3.07, 3.04* and 3.01 (4s, 6H, $2NCH_3$), 2.07*, 1.76 and 1.72* (3s, 6H, $2CH_3$), 1.45*, 1.44* and 1.42 (3s, 18H, 2OBu^t), 1.22-1.05 (m, 3H, OCH_2CH_3); IR: ν_{max} 3309, 3260, 3154, 1746, 1734, 1705, 1640, 1506 cm^{-1}; MS: *m/z* (%) 542 (2) [M$^+$], 411 (91), 355 (77), 311 (24), 298 (100). Anal. Calcd for $C_{23}H_{38}N_6O_7S$ (542.6): C, 50.91; H, 7.06; N, 15.49. Found: C, 51.12; H, 7.21; N, 15.57.

10e: 98% yield; d.r. 66:34; white solid from MeOH; ^{1}H-NMR: δ 9.54*, 9.36*, 9.30 and 9.26 (4s, 2H, 2NH), 6.30 and 6.18* (2br s, 4H, $CONH_2$), 5.13 and 4.53* (2s, 1H, CH), 3.62* and 3.58 (2s, 3H, OCH_3), 3.08*, 3.06 and 3.02* (3s, 6H, $2NCH_3$), 1.98, 1.78*, 1.76 and 1.74* (4s, 6H, $2CH_3$); IR: ν_{max} 3484, 3456, 3308, 3193, 1734, 1714, 1702, 1672, 1643, 1593 cm^{-1}. Anal. Calcd for $C_{14}H_{22}N_8O_5S$ (414.4): C, 40.57; H, 5.35; N, 27.04. Found: C, 40.72; H, 5.16; N, 27.21.

10f: 60% yield; d.r. 30:70; white solid from Et_2O-petroleum ether (40-60 °C); ^{1}H-NMR: δ 9.83 and 9.75* (2s, 1H, NH), 9.63 and 9.51* (2s, 1H, NH), 4.51* and 4.34 (2s, 1H, CH), 3.67-3.58 (m, 5H, OCH_3 and NCH_2CH_3), 3.31 (q, J = 7.0 Hz, 2H, NCH_2CH_3), 2.09*, 1.78 and 1.72* (3s, 6H, $2CH_3$), 1.46*, 1.44* and 1.42 (3s, 18H, 2OBu^t), 1.21-0.96 (m, 6H, $2NCH_2CH_3$); IR: ν_{max} 3312, 3243, 3151, 1748, 1717, 1702, 1644, 1509 cm^{-1}; MS: *m/z* (%) 556 (3) [M$^+$], 425 (41), 369 (27), 325 (25), 298 (100). Anal. Calcd for $C_{24}H_{40}N_6O_7S$ (556.7): C, 51.78; H, 7.24; N, 15.10. Found: C, 51.93; H, 7.43; N, 15.30.

10g: 97% yield; d.r. 43:57; white solid from MeOH; ^{1}H-NMR: δ 9.57*, 9.41*, 9.32 and 9.28 (4s, 2H, 2NH), 6.32 and 6.16* (2br s, 4H, $CONH_2$), 5.14 and 4.53*(2s, 1H, CH), 3.68-3.59 (m, 5H, OCH_3 and NCH_2CH_3), 3.30 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 1.98, 1.81*, 1.75 and 1.74* (4s, 6H, $2CH_3$), 1.20-0.97 (m, 6H, $2NCH_2CH_3$); IR: ν_{max} 3487, 3458, 3439, 3288, 3200, 1731, 1697, 1683, 1641, 1595 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_8O_5S$ (442.5): C, 43.43; H, 5.92; N, 25.32. Found: C, 43.21; H, 6.05; N, 25.12.

One-pot procedure for the synthesis of 2-thioxo-1,3,7-triazaspiro[4.4]non-8-en-4-one derivatives[20] (13a-g) and 5-oxo-4-(4-substituted 5-oxo-2-thioxoimidazolidin-4-yl)-2,5-dihydro-1*H*-pyrazole derivatives[20] (14-15a-c). 1,2-Diaza-1,3-butadienes **1a,e-h** (2 mmol) and **8a-b** (1 mmol) were dissolved in MeOH (20 mL) at room temperature. After both reagents had disappeared and the intermediates **10a-g** became the major components (monitored by TLC, ~0.5 h), THF (20 mL) was added to increase the solubility only in the cases in which a precipitate was formed during the reaction. The crude reaction mixture was then treated with NaH (1 eq.) and allowed to stand at room temperature until the total disappearance of **10a-g** was observed (monitored by TLC, 0.6-1 h). After removal of the solvent *in vacuo*, the crude reaction mixture was dissolved in H_2O (5 mL), neutralized with 2N HCl and extracted with EtOAc (3x40 mL). The combined organic layers containing **13a-g** were dried over Na_2SO_4, evaporated *in vacuo* and purified by flash-chromatography on a silica-gel column (eluent, ethyl acetate-methanol mixtures); **13a-g** were recrystallized from the appropriate solvents (see below). The recovered aqueous layer containing **14a-b** was evaporated to dryness *in vacuo*. The residue was suspended in MeOH (10 mL) at 0 °C and acidified by addition of TFA (0.5 mL) to afford directly **15a,b** as white powders with satisfactory purity. In the case of **14c**, the aqueous layer was

treated with 2N HCl up to pH ~4, saturated with NaCl and extracted with EtOAc (2x30 mL). The combined organic layers were dried over Na_2SO_4, evaporated *in vacuo* to yield crude **15c**, purified by recrystallization from the appropriate solvents. In order to isolate **14a-c**, the aqueous phase was evaporated *in vacuo* and recrystallization from the appropriate solvents was performed (see below). Compounds **13a,d,f** were obtained as mixtures of conformers, as revealed by DNMR experiments in DMSO-d_6 (293-353 K).[21]

13a: 97% yield; mp 179-183 °C dec from Et_2O-petroleum ether (40-60 °C); ^{1}H-NMR: δ 8.43 and 8.24 (2s, 1H, NH), 7.42 (s, 1H, NH), 6.11 (s, 1H, NH), 3.52 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 3.04 and 2.99 (2s, 3H, NCH_3), 2.20 and 2.16 (2s, 3H, CH_3), 1.45, 1.42 and 1.39 (3s, 18H, 2OBu^t), 1.10 and 1.07 (2s, 3H, CH_3); ^{13}C-NMR: δ 180.9, 172.6, 166.4, 163.3, 155.8, 155.0 and 154.2, 91.6 and 91.4, 87.3, 81.3 and 81.0, 80.2 and 80.1, 77.3, 50.9, 30.8 and 30.7, 28.3, 27.9, 27.7 and 27.6, 15.3 and 15.2, 11.5 and 11.4; IR: ν_{max} 3359, 3316, 3280, 1737, 1684, 1613 cm^{-1}; MS: *m/z* (%) 528 (6) [M$^+$], 397 (26), 341 (100), 297 (8), 284 (87). Anal. Calcd for $C_{22}H_{36}N_6O_7S$ (528.6): C, 49.99; H, 6.86; N, 15.90. Found: C, 50.13; H, 6.59; N, 16.07.

13b: 56% yield; mp 140-143 °C dec from CH_2Cl_2/*n*-pentane; ^{1}H-NMR: δ 9.81 (br s, 1H, NH), 9.34 (s, 1H, NH), 8.76 (s, 1H, NH), 7.66 (d, *J* = 2.4 Hz, 1H, NH), 7.52-7.22 (m, 8H, aromatic), 7.01-6.91 (m, 2H, aromatic), 5.83 (d, *J* = 2.4 Hz, 1H, NH), 3.98-3.80 (m, 2H, OCH_2CH_3), 3.24 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 2.13 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.04 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 181.0, 172.6, 167.4, 163.0, 155.8, 154.8, 139.8, 139.5, 128.7, 122.1, 121.7, 118.7, 118.4, 90.2, 87.3, 77.5, 58.6, 30.9, 28.2, 15.2, 14.2, 11.4; IR: ν_{max} 3363, 3328, 3306, 3212, 3142, 1746, 1715, 1682, 1640, 1600 cm^{-1}; MS: *m/z* (%) 580 (0.08) [M$^+$], 429 (35), 310 (46), 208 (69), 151 (100). Anal. Calcd for $C_{27}H_{32}N_8O_5S$ (580.7): C, 55.85; H, 5.55; N, 19.30. Found: C, 55.99; H, 5.68; N, 19.12.

13c: 44% yield; mp 157-162 °C dec from $CHCl_3$/*n*-pentane; ^{1}H-NMR: δ 8.53 (br s, 1H, NH), 7.09 (br s, 1H, NH), 6.37 (br s, 2H, $CONH_2$), 6.13 (s, 2H, $CONH_2$), 5.51 (s, 1H, NH), 3.94-3.74 (m, 2H, OCH_2CH_3), 3.18 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 2.15 (s, 3H, CH_3), 1.06-0.98 (m, 6H, CH_3 and OCH_2CH_3); ^{13}C-NMR: δ 181.0, 172.5, 168.1, 163.0, 159.1, 158.0, 89.7, 87.5, 77.4, 58.5, 31.0, 28.2, 15.3, 14.1, 11.5; IR: ν_{max} 3431, 3324, 3272, 3199, 1734, 1717, 1695, 1682, 1668, 1596 cm^{-1}; MS: *m/z* (%) 428 (0.06) [M$^+$], 353 (62), 310 (31), 251 (100). Anal. Calcd for $C_{15}H_{24}N_8O_5S$ (428.5): C, 42.05; H, 5.65; N, 26.15. Found: C, 42.21; H, 5.49; N, 26.31.

13d: 71% yield; mp 162-166 °C dec from THF/*n*-pentane; ^{1}H-NMR: δ 8.42 and 8.22 (2s, 1H, NH), 7.44 (s, 1H, NH), 6.11 (s, 1H, NH), 4.03-3.78 (m, 2H, OCH_2CH_3), 3.19 (s, 3H, NCH_3), 3.03 and 2.98 (2s, 3H, NCH_3), 2.20 and 2.17 (2s, 3H, CH_3), 1.45, 1.42 and 1.38 (3s, 18H, 2OBu^t), 1.10-0.98 (m, 6H, CH_3 and OCH_2CH_3); ^{13}C-NMR: δ 181.0, 172.8, 166.8, 162.6, 155.8, 155.0 and 154.3, 91.7 and 91.5, 87.3, 81.4 and 81.0, 80.2 and 80.1, 77.4, 58.9, 30.9 and 30.0, 28.3, 28.0, 27.8 and 27.7, 15.4 and 15.3, 14.1, 11.3 and 11.2; IR: ν_{max} 3351, 3326, 3245, 1740, 1731, 1704, 1617 cm^{-1}; MS: *m/z* (%) 542 (8) [M$^+$], 411 (30), 355 (100), 298 (49). Anal. Calcd for $C_{23}H_{38}N_6O_7S$ (542.6): C, 50.91; H, 7.06; N, 15.49. Found: C, 51.2; H, 7.15; N, 15.61.

13e: 49% yield; mp 180-184 °C dec from THF/*n*-pentane-Et_2O; ^{1}H-NMR: δ 8.53 (br s, 1H, NH), 7.06 (br s, 1H, NH), 6.33 (br s, 2H, $CONH_2$), 6.11 (s, 2H, $CONH_2$), 5.49 (s, 1H, NH), 3.48 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 2.14 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C-NMR: δ 180.9, 172.4, 167.6, 163.6, 159.1, 158.0, 89.6, 87.5, 77.4, 50.5, 31.0, 28.2, 15.2, 11.8; IR: ν_{max} 3442, 3330, 3275, 3200, 1743, 1732, 1717, 1696, 1682, 1668, 1596 cm^{-1}; MS: *m/z* (%) 414 (0.34) [M$^+$], 339 (64), 296 (17), 237 (100). Anal. Calcd for $C_{14}H_{22}N_8O_5S$ (414.4): C, 40.57; H, 5.35; N, 27.04; Found: C, 40.62; H, 5.49; N, 27.21.

13f: 78% yield; mp 150-153 °C dec from Et_2O-petroleum ether (40-60 °C); ^{1}H-NMR: δ 8.45 and 8.22 (2s, 1H, NH), 7.40 (s, 1H, NH), 6.15 (s, 1H, NH), 4.02-3.74 (m, 4H, $2NCH_2CH_3$), 3.50 (s, 3H, OCH_3), 2.21 and 2.18 (2s, 3H, CH_3), 1.46, 1.43 and 1.39 (3s, 18H, 2OBu^t), 1.16 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 1.07-0.98 (m, 6H, NCH_2CH_3 and CH_3); ^{13}C-NMR: δ 178.5, 172.2, 166.8, 163.3, 155.7, 155.0 and 154.2, 91.9 and 91.7, 87.6, 81.3 and 81.0, 80.2 and 80.1, 77.0, 50.5, 39.6, 36.4, 27.9, 27.7 and 27.6, 15.4 and 15.3, 12.6, 12.3, 11.4 and 11.3; IR: ν_{max} 3350, 3321, 3223, 1732, 1709, 1699, 1608 cm^{-1}; MS: *m/z* (%) 556 (5) [M$^+$], 425 (30), 369 (75), 298 (100). Anal. Calcd for $C_{24}H_{40}N_6O_7S$ (556.7): C, 51.78; H, 7.24; N, 15.10. Found: C, 51.93; H, 7.43; N, 15.20.

13g: 43% yield; mp 184-188 °C dec from THF-EtOAc/*n*-pentane; ^{1}H-NMR: δ 8.59 (br s, 1H, NH), 7.09 (br s, 1H, NH), 6.37 (br s, 2H, $CONH_2$), 6.13 (s, 2H, $CONH_2$), 5.53 (s, 1H, NH), 3.95-3.68 (m, 4H, $2NCH_2CH_3$), 3.45 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3), 1.16 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 1.02-0.97 (m, 6H, NCH_2CH_3 and CH_3); ^{13}C-NMR: δ 178.6, 172.0, 168.2, 163.7, 159.1, 158.0, 89.9, 88.0, 77.2, 50.2, 39.5, 36.3, 15.3, 12.8, 12.6, 11.7; IR: ν_{max} 3484, 3414, 3339, 3276, 3162, 1744, 1703, 1669, 1642, 1594 cm^{-1}; MS: *m/z* (%) 442 (0.04) [M$^+$], 367 (15), 308 (3), 237 (100). Anal. Calcd for $C_{16}H_{26}N_8O_5S$ (442.5): C, 43.43; H, 5.92; N, 25.32. Found: C, 43.57; H, 6.09; N, 25.51.

14a: mp 259-265 °C dec from CH_2Cl_2/*n*-pentane; ^{1}H-NMR: δ 12.52 (br s, 1H, NH), 9.97 (s, 1H, NH), 8.30 (s, 1H, NH), 7.53-6.94 (m, 10H, aromatic), 3.19 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 2.06 (s, 3H, CH_3), 1.74 (s, 3H, CH_3); ^{13}C-NMR: δ 179.8, 171.8, 164.3, 152.7, 150.1, 149.1, 145.2, 138.7, 138.6, 128.9, 122.6, 122.5, 119.1, 118.1, 85.8, 73.7, 31.7, 28.2, 14.1, 13.6; IR: ν_{max} 3464, 3361, 3202, 3136, 1712, 1693, 1589, 1571, 1542 cm^{-1}. Anal. Calcd for $C_{25}H_{25}N_8NaO_4S$ (556.6): C, 53.95; H, 4.53; N, 20.13. Found: C, 54.16; H, 4.61; N, 20.31.

14b: mp 222-226 °C dec from MeOH; ^{1}H-NMR: δ 9.42 (s, 1H, NH), 8.60 and 7.38 (2br s, 2H, $CONH_2$), 6.12 (br s, 2H, $CONH_2$), 3.15 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3), 1.93 (s, 3H, CH_3), 1.84 (s, 3H, CH_3); ^{13}C-NMR: δ 180.1, 171.4, 162.5, 156.7, 151.3, 148.6, 142.8, 90.1, 72.4, 31.8, 28.2, 13.5, 12.7; IR: ν_{max} 3488, 3341, 3288, 1748, 1739, 1722, 1679, 1592, 1559 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_8NaO_4S$ (404.4): C, 38.61; H, 4.24; N, 27.71. Found: C, 38.81; H, 4.11; N, 27.89.

14c: mp 218-222 °C dec from MeOH-EtOAc; ^{1}H-NMR: δ 9.43 (s, 1H, NH), 8.67 and 7.30 (2br s, 2H, $CONH_2$), 6.08 (br s, 2H, $CONH_2$), 3.99-3.89 (m, 1H, NCH_2CH_3), 3.80-3.70 (m, 2H, NCH_2CH_3), 3.33-3.22 (m, 1H, NCH_2CH_3), 1.92 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.11 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 0.85

(t, J = 7.2 Hz, 3H, NCH_2CH_3); ^{13}C-NMR: δ 178.6, 170.9, 162.6, 156.6, 151.0, 148.3, 142.5, 89.8, 72.4, 40.5, 36.1, 13.3, 12.7, 12.5, 12.4; IR: ν_{max} 3481, 3323, 3236, 1745, 1732, 1724, 1679, 1571, 1559 cm^{-1}. Anal. Calcd for $C_{15}H_{21}N_8NaO_4S$ (432.4): C, 41.66; H, 4.89; N, 25.91. Found: C, 41.83; H, 5.10; N, 26.13.

15a: 36% yield; mp 218-222 °C dec from MeOH; ^{1}H-NMR: δ 13.6 (br s, 1H, NH), 10.9 (s, 1H, NH), 10.1 (s, 1H, NH), 8.30 (s, 1H, NH), 7.59-7.28 (m, 8H, aromatic), 7.14 (t, J = 7.5 Hz, 1H, aromatic), 7.02 (t, J = 7.4 Hz, 1H, aromatic), 3.22 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 2.09 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C-NMR: δ 180.8, 170.2, 161.1, 152.6, 149.2, 146.0, 142.3, 138.5, 136.7, 129.1, 128.9, 124.2, 122.6, 119.8, 118.2, 93.8, 71.3, 31.8, 28.5, 13.4, 11.5; IR: ν_{max} 3371, 3290, 1750, 1716, 1682, 1645, 1601, 1561, 1542 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_8O_4S$ (534.6): C, 56.17; H, 4.90; N, 20.96. Found: C, 56.34; H, 4.75; N, 21.14.

15b: 26-28% yield; mp 215-220 °C dec from MeOH; ^{1}H-NMR: δ 13.14 (br s, 1H, NH), 9.51 (s, 1H, NH), 8.08 and 7.89 (2br s, 2H, $CONH_2$), 6.12 (br s, 2H, $CONH_2$), 3.16 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3), 2.00 (s, 3H, CH_3), 1.92 (s, 3H, CH_3); ^{13}C-NMR: δ 180.7, 170.6, 160.7, 156.8, 148.7, 148.4, 141.3, 94.4, 71.2, 31.8, 28.4, 13.4, 11.3; IR: ν_{max} 3470, 3308, 3171, 1738, 1714, 1700, 1667, 1587 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_8O_4S$ (382.4): C, 40.83; H, 4.74; N, 29.30. Found: C, 41.05; H, 4.59; N, 29.44.

15c: 20% yield; mp 172-178 °C dec from EtOAc-Et_2O/*n*-pentane; ^{1}H-NMR: δ 13.20 (br s, 1H, NH), 9.54 (s, 1H, NH), 8.12 and 7.92 (2br s, 2H, $CONH_2$), 6.14 (br s, 2H, $CONH_2$), 4.08-3.96 (m, 1H, NCH_2CH_3), 3.82-3.72 (m, 2H, NCH_2CH_3), 3.34-3.24 (m, 1H, NCH_2CH_3), 2.00 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.12 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 0.89 (t, J = 6.8 Hz, 3H, NCH_2CH_3); ^{13}C-NMR: δ 179.2, 170.2, 161.0, 158.6, 148.8, 148.2, 141.1, 94.0, 71.2, 40.6, 36.3, 13.4, 12.6, 12.5, 11.8; IR: ν_{max} 3465, 3320, 3213, 1742, 1720, 1717, 1699, 1585 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_8O_4S$ (410.5): C, 43.89; H, 5.40; N, 27.30. Found: C, 44.01; H, 5.59; N, 27.47.

Preparation of 2-(alkylimino)-1-thia-3,7-diazaspiro[4.4]non-8-en-4-one derivatives[20] (17a-c): To a suspension of **10c,e,g** as a diastereomeric mixture (1 mmol) in THF/H_2O (1/1 w/w) (20 mL) was added TFA (0.5 mL). The reaction mixture was refluxed until the complete conversion into **17a-c** as major components (monitored by TLC, 20-30 min). After removal of the organic solvent *in vacuo*, the remaining aqueous phase was saturated with NaCl, neutralized with $NaHCO_3$ and extracted with EtOAc (2x50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure, to yield crude **17a-c** which were purified by recrystallization from the appropriate solvents (see below).

17a: 70% yield; mp 177-182 °C dec from THF-Et_2O; ^{1}H-NMR: δ 8.24 (s, 1H, NH), 7.14 (s, 1H, OH), 6.38 (br s, 2H, $CONH_2$), 4.07-3.87(m, 2H, OCH_2CH_3), 3.08 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3), 2.15 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.06 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR: δ 173.1, 163.7, 163.1, 158.9, 153.3, 98.7, 94.4, 71.5, 58.8, 37.8, 28.8, 17.8, 14.0, 12.0; IR: ν_{max} 3491, 3375, 3171, 3095, 1702, 1631, 1574 cm^{-1}; MS: *m/z* (%) 371 (0.2) [M$^+$], 353 (2), 312 (0.2), 186 (100). Anal. Calcd for $C_{14}H_{21}N_5O_5S$ (371.4): C, 45.27; H, 5.70; N, 18.86. Found: C, 45.33; H, 5.79; N, 18.93.

17b: 68% yield; mp 180-183 °C dec from THF/*n*-pentane; ^{1}H-NMR: δ 8.26 (s, 1H, NH), 7.14 (s, 1H, OH), 6.36 (br s, 2H, $CONH_2$), 3.54 (s, 3H, OCH_3), 3.10 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 2.15 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C-NMR: δ 173.1, 164.2, 162.8, 158.9, 153.2, 98.5, 94.4, 71.5, 50.6, 37.9, 28.8, 17.8, 12.2; IR: ν_{max} 3480, 3358, 3165, 3094, 1715, 1700, 1632, 1614, 1576 cm^{-1}; MS: *m/z* (%) 357 (4) [M$^+$], 339 (21), 314 (18), 186 (100). Anal. Calcd for $C_{13}H_{19}N_5O_5S$ (357.4): C, 43.69; H, 5.36; N, 19.60. Found: C, 43.72; H, 5.41; N, 19.70.
NOE enhancement factors: OH{CH_3} 4%; NH{CH_3} 1%; CH_3{OH} 12%.

17c: 72% yield; mp 154-160 °C dec from EtOAc-Et_2O; ^{1}H-NMR: δ 8.22 (s, 1H, NH), 7.08 (s, 1H, OH), 6.37 (br s, 2H, $CONH_2$), 3.68-3.54 (m, 2H, NCH_2CH_3), 3.51 (s, 3H, OCH_3), 3.35-3.19 (m, 2H, NCH_2CH_3), 2.15 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 1.04 (t, J = 7.0 Hz, 3H, NCH_2CH_3); ^{13}C-NMR: δ 172.8, 164.1, 163.0, 158.9, 150.4, 98.6, 94.4, 71.1, 50.4, 45.9, 36.9, 17.6, 15.8, 12.1, 11.9; IR: ν_{max} 3451, 3341, 3309, 3195, 3122, 1703, 1671, 1642, 1610, 1590 cm^{-1}; MS: *m/z* (%) 385 (17) [M$^+$], 367 (15), 342 (61), 214 (100). Anal. Calcd for $C_{15}H_{23}N_5O_5S$ (385.4): C, 46.74; H, 6.01; N, 18.17. Found: C, 46.91; H, 6.23; N, 18.31.

Preparation of 5-substituted 1,3-dimethyl-5-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxoimidazolidin-4-one derivative[20] **(18)**: A suspension of **15b** (1 mmol) in MeOH (60 mL) was refluxed until a TLC check revealed its conversion into **18** (~12 h). The turbid solution was then concentrated under reduced pressure and the precipitate was filtered off to provide **18** as white powder in satisfactory purity. 94% yield; mp 231-234 °C dec from MeOH; ^{1}H-NMR: δ 11.71 (br s, 1H, NH), 10.22 (br s, 1H, NH), 9.50 (s, 1H, NH), 6.12 (br s, 2H, $CONH_2$), 3.17 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 1.92 (s, 6H, $2CH_3$); ^{13}C-NMR: δ 180.2, 171.0, 159.9, 156.6, 142.0, 138.9, 93.5, 71.3, 31.9, 28.2, 13.4, 10.6; IR: ν_{max} 3512, 3393, 3305, 1700, 1710, 1642, 1571, 1528 cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_7O_3S$ (339.4): C, 42.47; H, 5.05; N, 28.89. Found: C, 42.64; H, 5.16; N, 28.74.

Preparation of 1,3-dimethyl-5-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxoimidazolidin-4-one[20] **(19)**: To a suspension of **15b** (1 mmol) in THF/H_2O mixture (1/1 w/w) (20 mL) TFA (0.2 mL) was added. The reaction mixture was refluxed until the complete formation of **19** (10 h). After removal of the organic solvent under reduced pressure, the remaining aqueous layer was saturated with NaCl and neutralized with $NaHCO_3$. Extraction of crude product **19** was performed with EtOAc (2x50 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure and pure product **19** was obtained by recrystallization (92% yield) from the appropriate solvents (see below). Alternatively, **19** could be obtained directly from **18** with the same hydrolytic treatment (6 h) and subsequent work-up (91% yield). Mp 218-222 °C dec from THF-Et_2O; ^{1}H-NMR: δ 11.51 (br s, 1H, NH), 10.04 (br s, 1H, NH), 5.19 (s, 1H, CH), 3.14 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3), 2.05 (s, 3H, CH_3); ^{13}C-NMR: δ 181.0, 172.4, 159.7, 139.5, 92.6, 58.2, 31.6, 27.9, 9.5; IR: ν_{max} 3262, 1725, 1682, 1609, 1543, 1516 cm^{-1}; MS: *m/z* (%) 240 (100) [M$^+$]. Anal. Calcd for $C_9H_{12}N_4O_2S$ (240.3): C, 44.99; H, 5.03; N, 23.32. Found: C, 45.20; H, 5.15; N, 23.45.

Preparation of 2-(1-substituted ethylidene)-5,6-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-one derivatives[20] (21a-c) and 2-(1-substituted ethylidene)-6,7-dihydro-5*H*-thiazole[3,2-*a*]pyrimidin-3(2*H*)-one derivatives[20] (21d-f): To a stirred solution of **20a,b** (1 mmol) in MeOH (20 mL) was added dropwise a solution of 1,2-diaza-1,3-butadienes **1a,c** (1 mmol) in MeOH (10 mL) or **1e** (1 mmol) as solid portionwise over 15 min. The reaction mixture was allowed to stand at room temperature until it became pale yellow (**21a,d,e**) or cloudy (**21b,c,f**) (30-90 min). After removal of MeOH under reduced pressure **21a,d,e** were purified by recrystallization from the appropriate solvents (see below); **21b,c,f** were directly collected by filtration as white powders, after partial removal of MeOH *in vacuo*.

21a: 62% yield; mp 147-151 °C dec from EtOAc-MeOH-Et_2O; ^{1}H-NMR: δ 9.34 (br s, 2H, 2NH), 3.76 (s, 4H, $2CH_2$), 1.89 (s, 3H, CH_3), 1.45 (s, 9H, OBu^t); ^{13}C-NMR: δ 173.8, 165.5, 152.5, 149.0, 79.5, 66.8, 45.2, 27.9, 13.7; IR: ν_{max} 3460, 3380, 2632, 1739, 1605, 1594, 1569 cm^{-1}; MS: *m/z* (%) 298 (0.19) [M$^+$], 225 (0.66), 166 (60), 102 (100). Anal. Calcd for $C_{12}H_{18}N_4O_3S$ (298.4): C, 48.31; H, 6.08; N, 18.78. Found: C, 48.41; H, 6.22; N, 18.94.

21b: 36% yield; mp 181-185 °C dec from MeOH; ^{1}H-NMR: δ 9.29 (br s, 2H, 2NH), 3.76 (s, 4H, $2CH_2$), 3.68 (s, 3H, OCH_3), 1.90 (s, 3H, CH_3); IR: ν_{max} 3114, 3035, 2592, 1742, 1706, 1613, 1567, 1542 cm^{-1}; MS: *m/z* (%) 256 (11) [M$^+$], 225 (0.39), 167 (0.32), 102 (100). Anal. Calcd for $C_9H_{12}N_4O_3S$ (256.3): C, 42.18; H, 4.72; N, 21.86. Found: C, 42.25; H, 4.85; N, 22.00.

21c: 27% yield; mp 206-209 °C dec from MeOH; ^{1}H-NMR: δ 12.30 (s, 1H, NH), 9.46 (br s, 2H, 2NH), 7.50 (d, *J* = 7.7 Hz, 2H, aromatic), 7.32 (t, *J* = 7.8 Hz, 2H, aromatic), 7.01 (t, *J* = 7.3 Hz, 1H, aromatic), 3.79 (s, 4H, $2CH_2$), 2.00 (s, 3H, CH_3); IR: ν_{max} 3133, 3022, 1705, 1698, 1621, 1587, 1563 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_5O_2S$ (317.4): C, 52.98; H, 4.76; N, 22.07. Found: C, 53.09; H, 4.21; N, 22.19.

21d: 75% yield; mp 187-192 °C dec from EtOAc-MeOH; ^{1}H-NMR: δ 8.91 (br s, 2H, 2NH), 3.32-3.27 (m, 4H, $2CH_2$), 1.86-1.78 (m, 5H, CH_3 and CH_2), 1.45 (s, 9H, OBu^t); ^{13}C-NMR: δ 166.1, 165.1, 153.3, 149.0, 79.7, 67.0, 39.7, 28.0, 18.4, 18.2; IR: ν_{max} 3184, 3114, 1726, 1637, 1610, 1557 cm^{-1}; MS: *m/z* (%) 312 (1) [M$^+$], 256 (14), 212 (26), 181 (7), 116 (100). Anal. Calcd for $C_{13}H_{20}N_4O_3S$ (312.4): C, 49.98; H, 6.45; N, 17.94. Found: C, 50.09; H, 6.67; N, 18.07.

21e: 34% yield; mp 208-212 °C dec from EtOAc/*n*-pentane-Et_2O; ^{1}H-NMR: δ 8.93 (br s, 2H, 2NH), 3.68 (s, 3H, OCH_3), 3.33-3.27 (m, 4H, $2CH_2$), 1.86-1.78 (m, 5H, CH_3 and CH_2); IR: ν_{max} 3215, 3075, 1748, 1705, 1634, 1606, 1566, 1530 cm^{-1}; MS: *m/z* (%) 270 (1.21) [M$^+$], 239 (0.33), 181 (1), 116 (100). Anal. Calcd for $C_{10}H_{14}N_4O_3S$ (270.3): C, 44.43; H, 5.22; N, 20.73. Found: C, 44.61; H, 5.33; N, 20.85.

21f: 45% yield; mp 228-230 °C dec from MeOH; ^{1}H-NMR: δ 12.27 (s, 1H, NH), 8.98 (br s, 2H, 2NH), 7.50 (d, *J* = 7.7 Hz, 2H, aromatic), 7.31 (t, *J* = 7.8 Hz, 2H, aromatic), 7.01 (t, *J* = 7.3 Hz, 1H, aromatic), 3.35-3.30 (m, 4H, $2CH_2$), 1.96 (s, 3H, CH_3), 1.86-1.82 (m, 2H, CH_2); ^{13}C-NMR: δ 166.8, 164.5, 152.4, 149.2, 138.9, 128.9, 122.4, 118.8, 68.4, 39.9, 18.4, 13.5; IR: ν_{max} 3478, 3176, 3067, 2807, 1712, 1693, 1633,

1607, 1594, 1556 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N_5O_2S$ (331.4): C, 54.37; H, 5.17; N, 21.13. Found: C, 54.48; H, 5.31; N, 21.26.

Preparation of 2,2-disubstituted 6,7-dihydro-5*H*-thiazole[3,2-*a*]pyrimidin-3(2*H*)-one derivative[20] (**23**): 1,2-Diaza-1,3-butadiene **1e** (2 mmol) and **20b** (1 mmol) were dissolved in MeOH (20 mL). The red colour of the mixture rapidly disappeared and a solid precipitate was formed (15 min). After partial removal of the solvent *in vacuo*, **23** was filtered off as a diastereomeric mixture in satisfactory purity. A further amount of **23** was obtained by chromatographic separation of the mother liquor on a silica gel column (eluent, CH_2Cl_2-EtOAc mixtures). 84% yield; d.r. 41:59; white solid from MeOH; ^{1}H-NMR: δ 10.00*, 9.99*, 9.80 and 9.78 (4s, 2H, 2NH), 8.62 and 8.46* (2s, 1H, NH), 8.28* and 8.09 (2s, 1H, NH), 7.65-6.94 (m, 10H, aromatic), 5.49 and 5.04* (2s, 1H, CH), 4.05-3.25 (m, 6H, $2CH_2$ and OCH_2CH_3), 2.12, 1.95*, 1.92 and 1.91* (4s, 6H, $2CH_3$), 1.83-1.28 (m, 2H, CH_2), 1.20-1.02 (m, 3H, OCH_2CH_3); ^{13}C-NMR: δ 170.6 and 170.2, 170.0 and 168.8, 153.0 and 152.9, 152.8 and 150.3, 149.5 and 149.2, 146.7, 144.1, 143.9 and 143.2, 138.8 and 138.7, 138.6 and 138.5, 128.9 and 128.8, 128.6, 122.5, 119.0 and 118.9, 118.3 and 118.0, 65.5 and 64.2, 61.3, 55.7 and 55.2, 45.8 and 45.6, 40.7 and 40.6, 19.0 and 18.8, 18.5 and 16.6, 13.8 and 13.6, 13.5 and 13.4; IR: ν_{max} 3379, 3357, 3341, 3203, 1733, 1715, 1685, 1642, 1592, 1537 cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_8O_5S$ (592.7): C, 56.74; H, 5.44; N, 18.91. Found: C, 56.91; H, 5.62; N, 19.04

X-ray diffraction study of 6b: *Crystal data*: $C_{14}H_{15}N_3O_4S$, MW = 321.35, monoclinic, space group C2/c, a = 32.483(4), b = 4.831(3), c = 20.886(4) Å, β = 111.44(5)°, U = 3051(1) $Å^3$, Z = 8, D_c = 1.40Mg m^{-3}, F(000) = 1344, λ = 0.71069 Å, T = 298K, (Mo-Kα) μ = 0.234 mm^{-1}, crystal dimensions 0.20 x 0.70 x 0.40 mm. A total of 5999 reflections were collected (2682 unique, R_{int} = 0.0732). *Data collection and processing*: intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-Kα radiation, ω/2θ scan mode, range 2.03° < θ < 24.98°. The unit cell parameters were determinated by least-squares refinement on diffractometer angles for 25 automatically centered reflections 5.92° < θ < 10.34°. In the final refinement cycles 1699 reflections having I > 2σ(I) were used, with 143 parameters varied. In refinements were used weights in accord with the scheme $w = 1/[\sigma^2(F_o^2)+(0.0973P)^2+9.6233P]$ where $P = (F_o^2+2F_c^2)/3$. The hydrogen atoms were located by geometrical calculation and refined using a 'riding' model. The final agreement indices were R_1 = 0.0682 and wR_2 = 0.1677. Goodness of fit on F^2 = 0.980. Largest difference peak and hole was 0.622 and -0.660 $eÅ^{-3}$.

X-ray diffraction study of 13d: *Crystal data*: $C_{23}H_{38}N_6O_7S$, MW = 542.65, triclinic, space group P-1, a = 10.093(3), b = 13.711(3), c = 10.568(4) Å, α = 109.58(5), β = 103.35(5), γ = 87.01(4)°, U = 1340(2) $Å^3$, Z = 2, D_c = 1.345Mg m^{-3}, F(000) = 580, λ = 0.71069 Å, T = 298K, (Mo-Kα) μ = 0.174 mm^{-1}, crystal dimensions 0.40 x 0.50 x 0.30 mm. A total of 5473 reflections were collected (5166 unique, R_{int} = 0.0274). *Data collection and processing*: intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-Kα radiation, ω/2θ scan mode, range 2.10° < θ < 27.62°. The unit cell parameters were determinated by least-squares refinement on diffractometer angles for 25 automatically centered reflections 7.51° < θ < 12.04°. In the final refinement cycles 2737 reflections having I > 2σ(I) were used, with 274 parameters varied. In refinements were used weights in accord with the scheme w =

$1/[\sigma^2(F_o^2)+(0.1249P)^2+2.83P]$ where $P = (F_o^2+2F_c^2)/3$. The hydrogen atoms were located by geometrical calculation and refined using a 'riding' model. The final agreement indices were $R_1 = 0.0805$ and $wR_2 = 0.2124$. Goodness of fit on $F^2 = 1.029$. Largest difference peak and hole was 0.748 and -0.576 eÅ^{-3}. The structures were solved by direct method and refined by full-matrix least-squares on F^2, using the SHELXL program packages.[22,23]

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