Reactions of 2-Amino-2-thiazolines with Isocyanates and Isothiocyanates. Chemical and Computational Studies on the Regioselectivity, Adduct Rearrangement, and Mechanistic Pathways†

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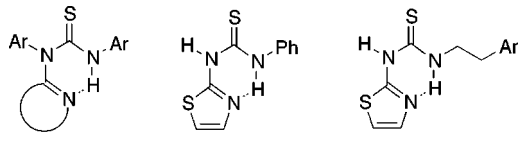
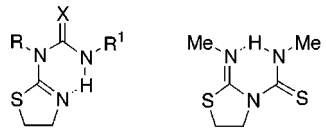
2-Amino-2-thiazoline derivatives bearing alkyl or aryl substituents at exocyclic nitrogen have been condensed with different isocyanates and isothiocyanates. The addition occurs at ring endocyclic nitrogen in a regiospecific manner to afford kinetic and enthalpy-favored adducts. The unequivocal assignment of these structures has been confirmed by X-ray diffraction analyses of several compounds. The endo adducts do not rearrange on heating with the sole exception of adducts in which the exocyclic nitrogen remains unsubstituted. Trapping experiments in the presence of other isocyanates or isothiocyanates produce the formation of new endo adducts by acyl exchange in the reaction mixture. Semiempirical PM3 calculations full corroborate the higher stability of endo or exo adducts depending on the substitution pattern. The formation of adducts is compatible with a stepwise reaction mechanism, for which semiempirical transition structures could be located in the potential energy surface, and the global energetics of the process have been determined. The formation of the endo adducts proceeds with a smaller activation barrier.

Introduction

The condensation of isocyanates and isothiocyanates with amino derivatives constitutes a simple and practical route for the preparation of diversely functionalized ureas and thioureas,[1] which may serve as potential chemotherapeutics. Aryl thioureas such as **1** have been extensively utilized as herbicides and also exhibit antifungical properties.[2] *N*-Phenyl-*N*′-(2-thiazolyl)thiourea (**2**) is an inhibitor of dopamine hydroxylase,[3] the key enzyme that mediates the conversion of dopamine into norepinephrine. Recently, phenethylthiazolyl thioureas (**3**) have emerged as a new class of nonnucleoside HIV-1 reverse transcriptase inhibitors.[4]



1 **2** **3**



4 **5**

Structures such as **4** have been the subject of enormous controversy, and the question of the regioselective functionalization of both nitrogen atoms at the 2-aminothiazoline moiety has not been definitively settled. The first thioureido adduct **4** (R = R′ = Me, X = S) or **5** was isolated by Gabriel as early as 1889 as a byproduct in the reaction of 2-bromoethylamine with methyl isothiocyanate.[5] Later, in 1928, German chemists reported that phenyl isothiocyanate adds to the endocyclic nitrogen of 2-amino-2-thiazoline (**6**) to form an adduct (**7**) which, upon heating, rearranges to the thioureido derivative **8**[6] (Scheme 1). Further reinvestigations of this research gave irreproducible and often contradictory results.[7] The selective attack at endocyclic or exocyclic nitrogen atoms of **6** as well as the structure of adducts, derived from phenyl isocyanate and phenyl isothiocyanate, were not clarified until 1986 when Rasmussen and co-workers pointed out the strict experimental conditions for rearrangement to

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† This work is dedicated respectfully to the memory of Wolfgang Oppolzer and his scientific family of co-workers over the years.

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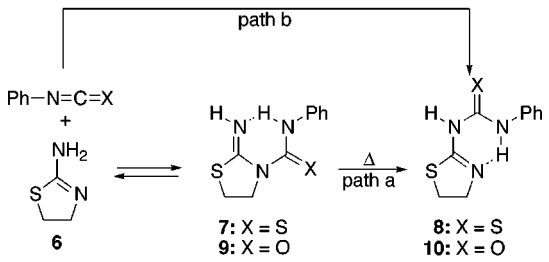
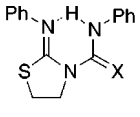
Scheme 1



occur.[8] While the X-ray structure of **8** had previously been determined,[9] these authors established the unequivocal structure of **9** by X-ray diffraction analysis.[10] The results were interpreted by assuming that the kinetic control adducts **7** and **9** may undergo a facile intramolecular rearrangement, even at low temperatures and in the solid state (path **a**), and/or dissociate to starting materials with further recombination at exocyclic nitrogen to yield the thermodynamically more stable products **8** and **10** (path **b**).

Given the inherent instability of endo adducts,[8] we[11] and others[12,13] have proposed that complex 2-amino-2-thiazolines derived from carbohydrates form adducts either with isocyanates or isothiocyanates by selective attack at exocyclic nitrogen. This rationale was also extended to the reaction of 2-arylamino-2-thiazolines with isocyanates and isothiocyanates to form exo adducts such as **4**.[14] Recently, this theory had to be retracted by determining unequivocally the structure of **11** by X-diffraction analysis.[15,16] Remarkably, these compounds did not undergo rearrangement under the attempted experimental conditions, either during fusion of neat **11** (or **12**) or after prolonged heating in solution. This suggests that these structures should therefore be the kinetic and thermodynamic control products.



11: X = S
12: X = O

Recently, Sakae and co-workers[17] reviewed the reaction of 2-bromoethylamine with methylisothiocyanate under mild conditions. Two byproducts, **4** (R = R′ = Me, X = S) and **5**, were isolated and their structures confirmed by X-ray crystallography. Thermal isomerization of **4** to **5** also was observed.

It appears evident from the above results that some intriguing points of this research have not yet been elucidated such as the regioselectivity in the attack of isocyanates and isothiocyanates to N-substituted thiazolines and how this substitution pattern affects the further rearrangement of adducts. Herein, we report an exhaustive study, corroborated by semiempirical calculations, on the endo/exo selectivity and the thermal stability of adducts, and attempts have also been undertaken to propose a mechanistic pathway consistent with our experimental observations. These results should certainly complement those of Rasmussen and his associates,[8] thereby gaining a further insight into this topic.

Results and Discussion

Synthesis and Structural Characterization. The general preparation of 2-alkyl(aryl)iminothiazolidine hydrochlorides **13a**−**c** has been previously reported,[15] and this can easily be accomplished by reaction of the corresponding amines with 2-chloroethyl isothiocyanate.[18] In our study, we have utilized these compounds as precursors for the preparation of adducts with isocyanates and isothiocyanates.

As previously mentioned, we have prepared adducts by condensing 2-aryliminothiazolidines with aryl iso(thio)cyanates.[15] These substances have the structure of *N*-aryl-2-arylimino-3-thiazolidincarboxamides and carbothioamides as in **11** or **12**, respectively, which do not rearrange to their exo counterparts. To ascertain whether substituents other than aromatic groups influence the rearrangement of such adducts, the reaction scope has been extended to include alkyl substituents as well. With this aim, hydrochlorides **13a**−**c** were reacted with alkyl or aryl isocyanates and isothiocyanates in pyridine solution to give, in most cases, crystalline adducts (**14** and **15**) in good yields. Carbothioamides **14a**−**d** show spectroscopic data analogous to those of **11**, thus confirming the analogy of these structures. The IR spectra show a strong band at ∼1620 cm^{-1} (C═N stretching) and a weaker one at ∼1550 cm^{-1} ascribable to the NH bending. The C═S stretching, however, could not be unequivocally established since it lies in the region of skeletal absorptions.[19] The fact that the diagnostic NH stretching does

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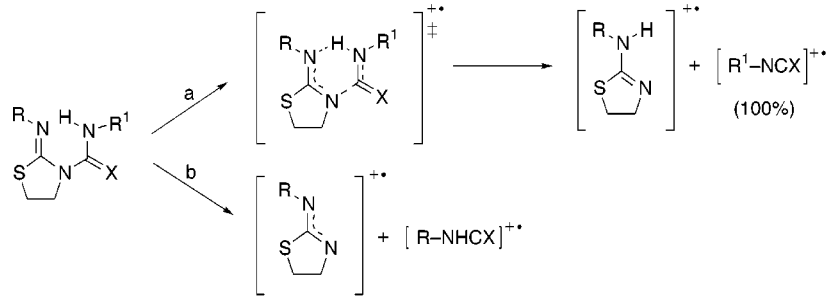
Scheme 2



not appear between 3400 and 3300 cm^{-1} as usual, but rather as a very weak and broad absorption at ~3100 cm^{-1}, suggests the participation of the NH group in an intramolecular hydrogen bonding. This is further confirmed by the strong downfield deshielding (11−13 ppm) of the NH proton. Similar chemical shifts have been reported for enamines[20] and thioureas[21] with intramolecular hydrogen bridges. These noncovalent bonds in compounds **14** and **15** form quasi six-membered rings, thus supporting the *Z* disposition for the C=N bond.

13a: R = Ph
13b: R = $(MeO)_2CHCH_2$
13c: R = *n*-Pr

14a: R = Ph, R^1 = 4-MeC_6H_4
14b: R = Ph, R^1 = Me
14c: R = $(MeO)_2CHCH_2$, R^1 = Me
14d: R = *n*-Pr, R^1 = Me

15a: R = Ph, R^1 = 3-$MeOC_6H_4$
15b: R = Ph, R^1 = 4-MeC_6H_4
15c: R = Ph, R^1 = Me
15d: R = $(MeO)_2CHCH_2$, R^1 = Ph
15e: R = *n*-Pr, R^1 = Ph
15f: R = $(MeO)_2CHCH_2$, R^1 = 4-MeC_6H_4

The methylene protons adjacent to the heterocyclic nitrogen are more deshielded than those vicinal to the sulfur atom ($\Delta\delta_H$ ~1.6 ppm). This deshielding should be attributed to the anisotropy of the thiocarbonyl group, close to that methylene and in opposite position to the hydrogen bonding. This is also evidenced by replacing the C=S group for the carbonyl, which causes a smaller deshielding between both methylenes ($\Delta\delta_H$ ~1.1 ppm for carboxamides **15**) and in full agreement with the lesser anisotropic effect of the C=O group.[22] Similar conclusions can be extracted from the ^{13}C NMR spectra. In particular, chemical shifts of the heterocyclic carbons are analogous to those of other 2-iminothiazolidines.[15,23]

Spectral data of carboxamides **15a**−**e** are equally in accordance with their structures. IR spectra show the additional amide band at ~1700−1650 cm^{-1}. The strong intramolecular hydrogen bonding also impedes the visualization of the NH stretching, weak and shifted toward lower wavenumbers. The ^{13}C resonance at ~151 ppm (C=O) is markedly different from that of the C=S group (~180 ppm) in carbothioamides, while analogous chemical shifts are found for the NC=N group (~158 ppm) and methylene carbons, with a smaller deshielding for NCH_2 as discussed above. Similar resonances for such methylenes (~49 and ~26 ppm for NCH_2 and SCH_2, respectively) have been described in other 2-iminothiazolidines having the exocyclic C=N bond.[23] This supports the endo structures attributed to compounds **15**, since such methylenes in the isomeric 2-amino-2-thiazolines, with a cocyclic C=N bond, resonate at ~59 and ~34 ppm.[23]

Mass spectra have also been performed to elucidate the structure and fragmentation pattern of compounds **14** and **15**. The intensities and the abundance of molecular ions are both enhanced by the use of an appropriate counterion (samples were treated with NaI solution) and ionization matrix using the fast-atom-bombardment mass spectrometry (FABMS). The peaks M + 1 and M + 23 could easily be detected in most spectra. As described for similar compounds,[7f,11b] the fragmentation patterns arise mainly from two decomposition routes (Scheme 2). Path **a** takes place through a McLafferty-type fragmentation[24] while route **b** involves the cleavage between the heterocyclic nitrogen and the (thio)carbonyl group. Both of them originate the most abundant peaks, which undergo subsequent fragmentations. In general, the most abundant peak is attributable to the isocyanate or isothiocyanates coming from the McLafferty fragmentation. It should be noted that structures with alkyl groups on both exocyclic nitrogen atoms (e.g., **14c**, **14d**) fragment mainly following the pathway **a**, with M + 1 as the most abundant peak. The regioisomeric exo adducts, if present, would give a similar fragmentation pattern.[7d]

In addition, the structure of carboxamide **15a** has been unequivocally determined by X-ray diffractometry,[25] which confirms the unifying character of endo adducts in this type of reactions. Single-crystal X-ray data (Supporting Information, Figure S1) reveal the same structure as that suggested by the NMR parameters. The five-membered ring is slightly twisted from an envelope

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conformation. Atoms C3 and C2 are 0.218 and 0.314 Å above and below the plane of atoms S, C(1), and N(1), respectively. The angle between the planes of both phenyl groups is 62.6°. The molecules are linked by intramolecular hydrogen bonds between N(3)−H(3a) and N(2) being the length N(3)···N(2) 2.698(2) Å and the angle N(3)−H(3a)−N(2) 138.5(1)°.

For comparative purposes, the X-ray diffraction analysis of compound **10** has also been accomplished, and a view with the crystallographic numbering scheme is shown in the Supporting Information (Figure S2). Although the structure of its thioanalogue **8** was established in 1970 by X-ray crystallography,[9] in that time the tautomeric composition of **8** could not be distinguished. Compound **10** is a rearranged product with a cocyclic C−N double bond, which evidences the rapid rearrangement of adducts having no alkyl or aryl substituent at exocyclic nitrogen. The thiazoline moiety appears in an envelope conformation in which the carbon atom C(3) is placed 0.392 Å above the plane occupied by the other four atoms of the ring. The X-ray crystal structure is consistent wich a structure of thiazoline and not of iminothiazolidine. The C(1)−N(endo) bond distance (1.262 Å) corresponds to a double bond, and it is shorter than the observed C(1)−N(exo) separation (1.378 Å). There is an intramolecular hydrogen bonding between N(3)−H(6) and N(1) [N(3)···N(1) 2.716(2) Å; N(3)−H(6)−N(1) 136.6-(1)°]. The molecules are also linked by intermolecular N(2)−H(5)···O hydrogen bonds [N(2)···O 2.821(2) Å; N(2)−H(5)−O 171.4(1)°]. Selected bond length and bond angles for **10** and **15a** are recolleted in the Supporting Information (Table S1).

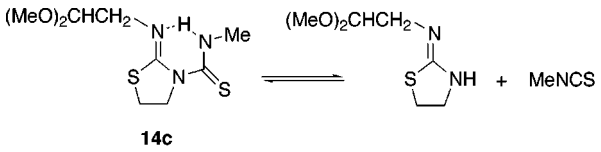
It is noteworthy that the solid-state structure of **10** differs considerably from that of its thioanalogue **8**. The s-trans,s-trans conformation found for the phenylureido moiety in the crystalline structure of **10** should be attributed to the intramolecular hydrogen bonding N−H···N(endo), stronger than the intramolecular nonbonded interaction S···O (1,5-intra mode), which has its origin in $n_{(C=O)} \rightarrow \sigma^*_{(C-S)}$ orbital overlap effect.[26] In stark contrast, the intramolecular 1,5-type S···S interaction should largely be responsible for the preferential s-cis arrangement of **8** in the solid state, as evidenced by the short intramolecular distance (3.0 Å) between the two sulfur atoms[9] ($r_{vw(S)} = 1.85$ Å).

Isomerization Experiments. To ascertain whether 2-iminothiazolidine derivatives with N-substituents other than hydrogen at exocyclic nitrogen are susceptible to rearrange upon heating, some carbothioamides and carboxamides were melt or refluxed in benzene solution. After cooling and/or solvent evaporation, the resulting residues were dissolved in $CDCl_3$ and monitored by ^{1}H NMR.

We have learned that adducts in which both exocyclic nitrogen atoms bear aryl substituents do not isomerize to exo adducts.[15] Similarly, adducts **15d** and **15e** did not undergo the rearrangement to exo adducts. Thus, **15d** was recovered unaffected and gave a clear ^{1}H NMR spectrum, and **15e** showed a minor decomposition to the starting alkyliminothiazolidine without evidencing the formation of an exo adduct.

In the case of carbothioamide **14c**, with an alkyl substituent at the iminic nitrogen, the ^{1}H NMR spectrum of a sample subjected to prolonged refluxing consists of a ∼1:1 mixture of the iminothiazolidine and MeNCS. The regioisomeric exo adduct, however, could not be detected. These results are consistent with a dissociation/recombination process as depicted in Scheme 3.

Scheme 3



14c

Scheme 4

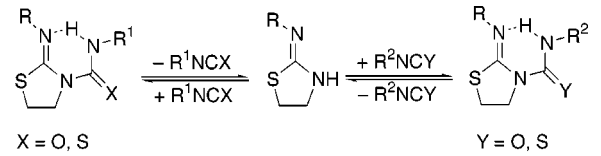


Table 1. Trapping Experiments of Adducts 11 and 12 with Some Iso(thio)cyanates[a,b]

compd	PhNCO	PhNCS	4-MeC$_6$H$_4$-NCO	4-MeC$_6$H$_4$-NCS	MeNCO	MeNCS
11	+		*c*	+	+	+
12		−	+	*c*	+	−

[a] In refluxing benzene. [b] Signs + and − indicate positive and negative tests, respectively. [c] Not determined.

Volatile isocyanates or isothiocyanates, such as MeNCS or MeNCO,[27] can be partly eliminated on heating, yielding an equimolar amount of the free iminothiazolidine. With nonvolatile isocyanates or isothiocyanates (e.g., PhNCO), the recombination path is essentially complete and the ^{1}H NMR spectrum of the recovered material is coincidental with that of the starting endo adduct. The preceding experiments indicate that endo adducts bearing alkyl or aryl substituents at the iminic nitrogen atom do not rearrange at all.

Trapping Experiments. To get further evidence on a dissociation/recombination mechanism, trapping experiments have also been achieved. When an endo adduct is heated in the presence of an equimolar amount of another isocyanate or isothiocyanate, the reaction mixture may eventually contain a new adduct in which the latter isocyanate or isothiocyanate may replace the former (Scheme 4).[28]

Adducts **11** and **12** were refluxed with different alkyl and aryl iso(thio)cyanates, and reaction mixtures were analyzed by TLC and NMR spectroscopy. Results are summarized in Table 1, indicating the cases in which the thiazolidine ring was captured by the added heterocumulene. Table 2 collets the energetics of these transformations evaluated by PM3 calculations (vide infra).

Thus, the resulting crude of **11** plus PhNCO consisted of a 3:2 mixture (by ^{1}H NMR integration) of adducts **11**

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(27) Methyl isocyanate is believed to be the main hazardous agent released in the sadly famous Bhopal incident. For an excellent chemical investigation of this issue see: D'Silva, T. D. J.; Lopes, A.; Jones, R. L.; Singhawangcha, S.; Chan, J. K. *J. Org. Chem.* **1986**, *51*, 3781−3788.

(28) (a) Klayman and co-workers once described the replacement of PhNCO by 1-naphthyl isothiocyanate in the exo adduct derived from 2-amino-2-thiazoline (ref 7d). (b) Similar replacement in 2-amino-2-oxazolines derivatives were described: Bosc, J. J.; Jarry, C.; Ouhabi, J.; Laguerre, M.; Carpy, A. *Can. J. Chem.* **1996**, *74*, 1341−1347. (c) For other acyl groups rearrangement: Kaugars, G.; Martin, S. E.; Nelson, S. J.; Watt, W. *Heterocycles* **1994**, *38*, 2593−2603.

Table 2. Reaction Enthalpies for Trapping Experiments

entry	R	X	R^1	Y	ΔH_R[a] (kcal mol^{-1})
1	Ph	S	Ph	O	−20.45
2	Ph	S	Me	O	−19.56
3	Ph	S	Me	S	−1.21
4	Ph	O	Me	S	+19.24
5	Ph	O	Me	O	+0.89
6	Me	S	Ph	O	−18.79
7	Me	O	Me	O	−0.63

[a] Determined by PM3 calculations.

and **12**, evidencing that the starting adduct releases PhNCS and 2-phenyliminothiazolidine being the latter trapped by the isocyanate (Table 2, entry 1). The proton spectrum shows two NH resonances, at 14.06 and 12.00 ppm, characteristic of both adducts, and different resonances for the NCH_2 groups ($\Delta\delta = 0.52$ ppm, vide supra). In the presence of 4-MeC_6H_4NCS, the resulting spectra consisted of two and very similar signal sets attributable to adducts **11** and **14a**.

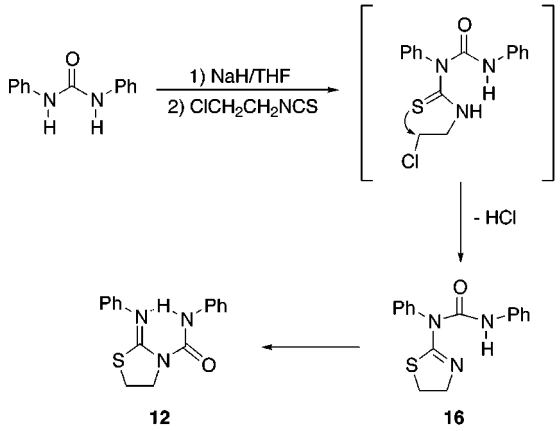
On the contrary, reaction of **11** with MeNCO led almost exclusively to the formation of **15c**. The ^1H and ^{13}C NMR spectra of the crude reaction were identical to those of an authentical sample of **15c**. Neither the deshielded NCH_2 methylene (at ∼4.9 ppm) nor the thiocarbonyl resonance (at ∼180 ppm) could be detected, thus discarding the recombination pathway with PhNCS. This result evidences the greater stability of isocyanate-based adducts than those derived from isothiocyanates (Table 2, entry 2). The reaction of **11** with MeNCS gave a mixture ∼1:3 of adducts **11** and **14b.** This also agrees with the enhanced stability of adducts derived from alkyl isothiocyanates with respect to their aromatic counterparts (Table 2, entry 3).

Experiments with **12** gave positive results with isocyanates only and failed with isothiocyanates (Table 2, entry 4 and inverse of entry 1). The crude reaction of **12** plus 4-MeC_6H_4NCO consisted of an almost 1:1 mixture of **12** and **15b**. Again, the reaction of **12** with MeNCO afforded the adduct **15c**. In this case, however, the ^1H NMR spectrum also detected a second byproduct, *N*,*N*′-dimethylurea (δ_{NH} = 4.43 ppm, δ_{CH3} = 2.79 ppm), generated presumably by reaction of MeNCO with traces of moisture.

To test whether the dissociative pathway also works with adducts containing alkyl substituents, compound **15d** was subjected to the aforementioned conditions in the presence of 4-MeC_6H_4NCO to give a ∼1:2 mixture of both adducts, **15d** and **15f**.

The preceding experiments prove once again that endo adducts derived from *N*-alkyl- or aryliminothiazolidines and isocyanates or isothiocyanates are the kinetic and thermodynamic control products without further tendency to isomerize. This does not mean, at least a priori, that exo adducts cannot be obtained by an indirect method. It is known that heterocyclic NH groups can be efficiently acylated by haloalkyl isothiocyanates in the presence of base.[18b] Accordingly, we reasoned that isomeric structures **16** could be obtained from *N*,*N*′-diphenylurea and 2-chloroethyl isothiocyanate, thus forming a transient 2-chloroethylthiourea that cyclizes intramolecularly by a S_N2 pathway (Scheme 5).

Scheme 5



The reaction was unsuccessful in pyridine solution as well as in a mixture of pyridine−Et_3N under reflux since deprotonation could not be achieved. However, treatment of *N*,*N*′-diphenylurea with NaH in THF solution and subsequent dropwise addition of 2-chloroethyl isothiocyanate afforded a crystalline, chromatographically homogeneous compound having the same spectral data of the rearranged compound **12**. Furthermore, ^1H NMR spectra of **12** were obtained by performing the reaction in THF-d_8 at −20 °C, immediately recording the spectra at that probe temperature, and then at regular intervals from that temperature to ambient temperature. NMR spectra verified the presence of **12** whereas resonances ascribable to the protons of **16** could not be identified.

Theoretical Rationalization. By far the experimental results of the reactions of 2-amino-2-thiazolines (or their tautomeric 2-iminothiazolidines) with isocyanates or isothiocyanates can be summarized as follows: (a) adducts with isocyanates are more stable than those of isothiocyanates; (b) the attack of heterocumulenes occurs regiospecifically at endocyclic nitrogen to give the endo adducts as the kinetically favored products; (c) if the exocyclic nitrogen is unsubstituted, the endo adducts rearrange to form the exo ones; (d) no rearrangement occurs if the exocyclic nitrogen is substituted. A theoretical study using PM3[29] semiempirical calculations was accomplished to justify the reactivity and regiochemical outcome as well as the stability of adducts. It is fair to say that related studies on the reaction of 2-amino-2-oxazolines with isocyanates and isothiocyanates have also been carried out at a semiempirical level too.[28b]

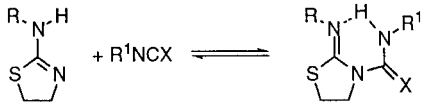
(a) Adduct Formation. The first issue to be addressed concerns the energetic profile of reactions of 2-iminothiazolidine derivatives with iso(thio)cyanates. Energetics data of semiempirical calculations (PM3) collected in Table 3 indicate the higher stability of adducts derived from isocyanates than their sulfur counterparts. Likewise, reactions with alkyl isocyanates or isothiocyanates usually yield more stable adducts than with aryl ones.

When a DFT calculation (B3LYP/6-31G*)[30] of a pair of representative isocyanate and isothiocyanate adducts

(29) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

(30) (a) Parr, R. G.; Yang, W. *Density Funtional Theory of Atoms and Molecules*; Oxford University Press: Oxford, 1989. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (c) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785−789. (d) Baerends, E. J.; Gritsenko, O. V. *J. Phys. Chem. A* **1997**, *101*, 5383−5403.

Table 3. Reaction Enthalpies for Adducts Formation



R	R^1	X	ΔH_R[a] (kcal mol^{-1})
H	H	O	−20.59
H	Me	O	−17.79
H	Ph	O	−17.15
Me	H	O	−24.81
Me	Me	O	−22.19
Me	Ph	O	−21.60
Ph	H	O	−23.38
Ph	Me	O	−20.52
Ph	Ph	O	−21.41
H	H	S	−3.00
H	Me	S	0.47
H	Ph	S	1.73
Me	H	S	−7.52
Me	Me	S	−4.03
Me	Ph	S	−2.81
Ph	H	S	−5.69
Ph	Me	S	−2.17
Ph	Ph	S	−0.96

[a] Determined by PM3 calculations.

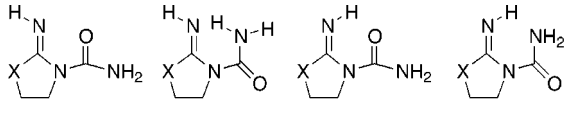
Table 4. Relative Stability (kcal mol^{-1}) of Adducts 18−25

X	**18**[a]	**19**	**20**	**21**	**22**	**23**	**24**	**25**
S	0.00	+3.56	+3.08	+0.49	−1.48	−3.61	−3.77	−1.35
O	0.00	+4.17	+3.37	+1.68	−2.46	−2.64	−3.92	−0.16

[a] Energies are arbitrarily referred to this structure.

(R = R^1 = Me; Table 3) was developed, the same order of stability was observed, validating our semiempirical results.[31]

(b) Adduct Rearrangement. Second, the conformational or tautomeric stability of adducts should be analyzed. With this goal, a series of simplified models, also applicable to oxazoline derivatives, have been computerized semiempirically. In the case of endo adducts, not only the conformer **18** should be considered, but also **17**, **19**, and **20**, despite X-ray diffraction data,[8,15,16] support a *Z* stereochemistry for the C=N double bond, and the intramolecular hydrogen bridge causes an s-trans disposition around the N−CX bond. This intramolecular bonding cannot be established in the alternative s-cis conformer **17**. Furthermore, the PM3 calculations could not locate any minimum for the latter structure, which evolved into **18**. Table 4 also shows that the *E* isomers **19** and **20** are appreciably less stable than **18**.



17 (*Z-s-cis*) **18** (*Z-s-trans*) **19** (*E-s-cis*) **20** (*E-s-trans*)

For exo adducts, eight possible structures have been considered (**21**−**28**). Structures **23**−**26** are geometrically compatible with an intramolecular hydrogen bonding, while the tautomeric forms **21** and **22** exhibit the skeletal disposition of the exo adduct **8**[9] and **23** that of **10**, both of them determined by X-ray analysis. As before, theoretical calculations were unable to locate minima for

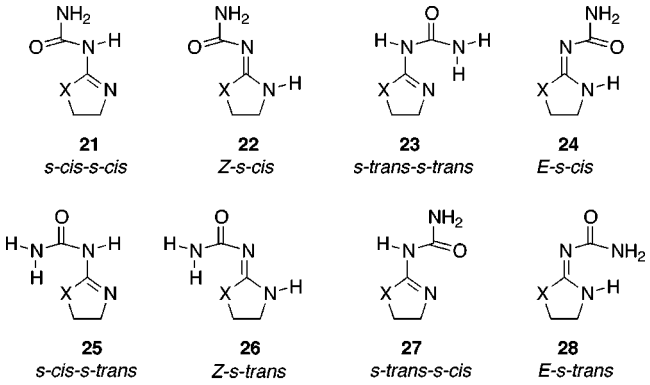
(31) DFT results: ΔH_R = −24.52 kcal mol^{-1}, X = O and −19.14 kcal mol^{-1}, X = S.

Table 5. Relative Stabilities (kcal mol^{-1}) of Compounds 29−39

compd	**a**	**b**	**c**
29[a]	0.00	0.00	0.00
30	+3.08	+3.51	+3.39
31	+3.56	+4.10	+4.12
32	−3.61	−3.66	−3.87
33	−1.35	−1.86	−1.42
34	+0.49	+0.37	−0.52
35	+0.49	+0.30	+1.12
36	−1.48	−0.92	−1.88
37	−1.48	−2.15	−1.76
38	−3.77	−3.26	−3.60
39	−3.77	−2.67	−2.87

[a] Energies are abitrarily referred to this structure.

26−**28**, and in fact, the simulated study provided the alternative structures **22**−**24**, respectively.

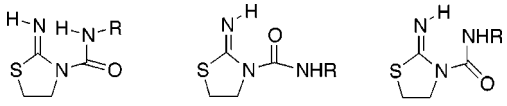


21 *s-cis-s-cis* **22** *Z-s-cis* **23** *s-trans-s-trans* **24** *E-s-cis*

25 *s-cis-s-trans* **26** *Z-s-trans* **27** *s-trans-s-cis* **28** *E-s-trans*

Table 4 collects the potential energy differences of compounds **18**−**25**, referred arbitrarily to **18**, which were determined with the PM3 Hamiltonian. These data reveal that exo adducts **22**−**25** are more stable than the endo structure **18**, whereas structures **19**−**21** are energetically disfavored. The energy differences between the structures of endo and exo adducts lie in the average range ∼1.5−4.0 kcal mol^{-1}, which justifies the rearrangement of the former to the more stable exo adducts.

Next, we have tried to rationalize the influence of substituents at exocyclic nitrogen atoms on the stability of adducts. With this aim, different substitution patterns have been considered for frameworks **29**−**41**.

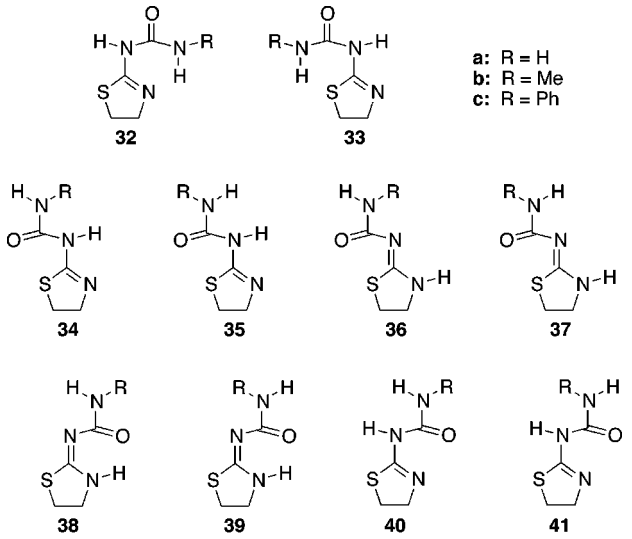


29 **30** **31**

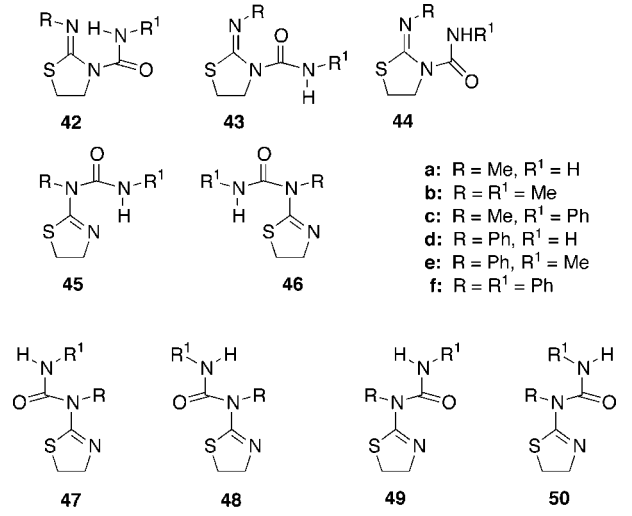
a: R = H
b: R = Me
c: R = Ph

Table 5 summarizes the energy differences for compounds **29**−**39**, evidencing the greater stability of exo adducts **32**, **33**, and **36**−**39** with respect to their endo counterparts **29**−**31**.[28b] Again, no minima were obtained for **40** and **41** at this theory level, and both structures evolved into **32**.

These results clearly corroborate the experimental works by Yamamoto and co-workers,[7i] who demonstrated the transformation of the structure **29b** into **32b**, and by Rasmussen et al.,[8] who pointed out the easy rearrangement of **9** (structure **29c**) to the exo adduct **10** (structure **32c**).



When the exocyclic nitrogen atom of the heterocycle is also substituted, the computational estimation of energies differs considerably from the above results, as evidenced in Table 6 for model compounds **42**−**50**. Structures as **36**−**39** cannot be adopted when $R^1 \neq H$ and were ruled out.



The search for true minima in the case of **49a**, **49b**, and **50a** resulted in the location of the corresponding adducts **45**. The endo adducts **42** become both the kinetic and thermodynamic control products with no tendency to convert into exo adducts. Thus, compounds **12** and **15c** (structures **42f** and **42e**, respectively) do not undergo rearrangement after prolonged heating. Substances with alkyl substituents on the nitrogen atom attached to C-2 do not rearrange either as evidenced by the experiments of Yamamoto and co-workers[7f,7i] with structure **42b** and those of the present work.

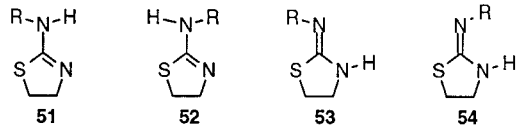
(c) Regiochemistry. The Mechanistic Pathways. It would be desirable to have an additional assessment of the endo regiospecificity observed in this type of reactions. The postulates of the frontier molecular orbital (FMO) theory offer a simple, often satisfactory, approach to evaluate the regioselectivity of numerous organic reactions.[32] This might also give some insight into the reaction outcome. There are two possible scenarios. The adducts could have been formed by a concerted pericyclic mechanism with a six-electron cyclic transition state (TS),

Table 6. Relative Stability (kcal mol^{-1}) of Compounds 42−50

compd	a	b	c	d	e	f
42[a]	0.00	0.00	0.00	0.00	0.00	0.00
43	+4.77	+4.78	+4.45	+3.34	+3.00	+4.18
44	+4.36	+4.48	+4.63	+3.35	+3.33	+6.17
45	+2.59	+2.82	+2.86	+4.49	+5.86	+7.51
46	+5.16	+4.54	+5.16	+7.24	+7.10	+8.79
47	+6.39	+6.59	+6.39	+5.54	+7.48	+8.59
48	+6.39	+6.28	+6.42	+5.54	+5.36	+6.91
49	+2.59	+2.82	+3.65	+6.00	+4.42	+5.96
50	+2.59	+5.66	+4.31	+6.00	+5.80	+5.59

[a] Energies are abitrarily referred to this structure.

Table 7. Relative Stability (kcal mol^{-1}) of Structures 51−54

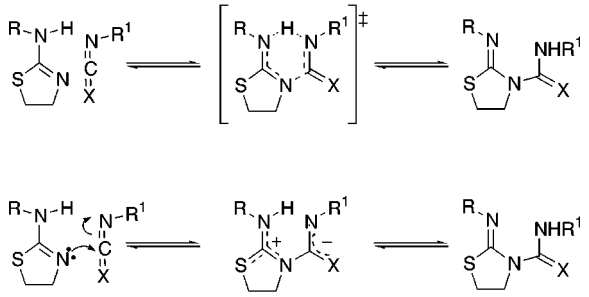


a R = H
b R = Me
c R =Ph

compd	a	b	c
51[a]	0.00	0.00	0.00
52	0.00	−0.01	+0.35
53	+3.02	−1.48	−0.12
54	+4.55	−0.01	−0.21

[a] Energies are abitrarily referred to this structure.

Scheme 6



equivalent to a $[(2\sigma + 2\pi) + 2\pi]$ ene reaction from a formal standpoint. The second possibility is a stepwise mechanism involving the intermediacy of dipolar species (Scheme 6).

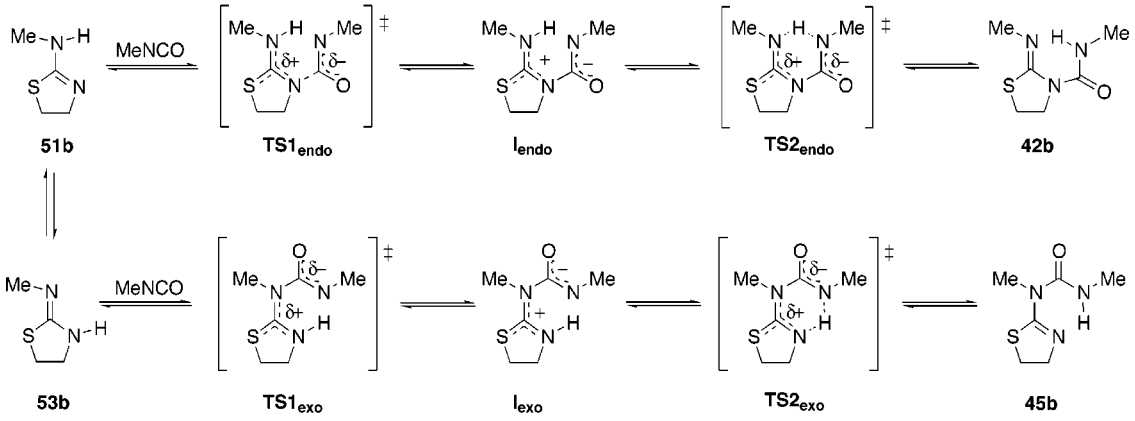
In a concerted mechanism, the formation of endo adducts arises from 2-amino-2-thiazoline tautomers while the 2-iminothiazolidine forms lead to exo adducts. This pathway suggests an explanation for the reversibility observed in adducts of 2-amino-2-thiazoline with phenyl isocyanate or isothiocyanate and the McLafferty-type fragmentation[24] (a retro-ene process) of adducts detected by mass spectrometry.

First, the relative stability of the possible conformers and tautomers of 2-amino-2-thiazoline and its *N*-methyl and *N*-phenyl derivatives was examined. A PM3 semiempirical calculation on structures **51**−**54** is shown in Table 7.

The reactive tautomers capable of undergoing a pericyclic mechanism (Scheme 6) should be **51** and **53**. It

(32) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. (b) Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*; Cambridge University Press: London, 1979.

Scheme 7



should also be noted that **51** (or **52**) become the most stable tautomers when R = H, whereas the iminothiazolidines **53** and **54** are energetically favored if R = Me or Ph, respectively. Bearing this in mind, our next target was to evaluate the energy of FMOs of the heterocycles and heterocumulenes (Table S2).

Energy values for HOMOs/LUMOs of reactants allow us the determination of $\Delta E_1 = \mathrm{HOMO}_{\mathrm{heterocycle}} - \mathrm{LUMO}_{\mathrm{heterocumulene}}$ and $\Delta E_2 = \mathrm{HOMO}_{\mathrm{heterocumulene}} - \mathrm{LUMO}_{\mathrm{heterocycle}}$, according to the FMO approach.[32] A simple inspection of data obtained (see Supporting Information) reveals that $\Delta E_1 < \Delta E_2$ in most cases, and this leads to consider the $\mathrm{HOMO}_{\mathrm{heterocycle}}/\mathrm{LUMO}_{\mathrm{heterocumulene}}$ interaction as prevalent, although figures for phenyl isocyanate and phenyl isothiocyanate result in comparable magnitudes of ΔE_1 and ΔE_2.

The AO coefficients at endocyclic nitrogen of 2-amino-2-thiazoline derivatives are very similar to those of 2-iminothiazolidines at their exocyclic nitrogen, so that the exclusive or preferential formation of *endo* adducts cannot be rationalized in terms of the FMO theory assumptions (Table S3).

As mentioned above, a stepwise process should not be ruled out. Bosc and co-workers have rationalized the *endo* addition of aryl isocyanates to 2-amino-2-oxazolines based on the higher reactivity index of endocyclic nitrogen atom.[33] The reactivity index is defined as electronic density of an atom in the HOMO, in other words, $2(c_i^{\mathrm{HOMO}})^2$ being c_i the AO coefficient of the atom considered. Although the computation was achieved with a simple CNDO/2 method, this result explains the selective attack of an isocyanate at the endocyclic nitrogen. However, the higher PM3 calculation of 2-amino-2-thiazolines gives similar reactivity indexes at endocyclic and exocyclic nitrogen atoms. Given the dipolar character of intermediates in a stepwise addition, not only the orbital contribution but also the Coulombic interactions must be added to the energy balance, being favored the attack from the more negative center of the heterocycle to the positive center of the heterocumulene. However, the consideration of this parameter could not differentiate between endo and exo approaches.

The evaluation of the energy changes, e.g. activation and reaction energies, for the concerted and stepwise reactions has also been performed. Calculations were carried out on a simplified reaction of both tautomers of 2-methylamino-2-thiazoline (**51b** and **53b**) with methyl isocyanate (Scheme 7). However, attempts to locate the transition structures of the concerted path were unsuccessful.

Table 8. Heat of Formation (kcal mol^{-1}) and Bond Distances (Å) for the Endo Adduct Process

entry		51b	MeNCO	TS1	I	TS2	42b
1	ΔH_f	20.14	−18.56	11.67	2.88	6.63	−20.61
2	$d_{N_{endo}\cdots C(O)}$			2.09	1.52	1.50	1.46
3	$d_{N(CO)\cdots C(O)}$		1.26	1.30	1.35	1.37	1.42
4	$d_{N(CO)\cdots H}$			1.82	1.69	1.43	1.01
5	$d_{N_{exo}\cdots H}$	1.00		1.02	1.06	1.25	1.90
6	$d_{C2\cdots N_{exo}}$	1.42		1.39	1.35	1.33	1.30
7	$d_{C2\cdots N_{endo}}$	1.31		1.33	1.38	1.40	1.44
8	$d_{N_{exo}\cdots N(CO)}$			2.72	2.55	2.50	2.70

Table 9. Heat of Formation (kcal mol^{-1}) and Bond Distances (Å) for the Exo Adduct Process

entry		53b	MeNCO	TS1	I	TS2	45b
1	ΔH_f	18.66	−18.56	11.89	5.07	8.99	−17.49
2	$d_{N_{exo}\cdots C(O)}$			2.06	1.54	1.51	1.47
3	$d_{N(CO)\cdots C(O)}$		1.26	1.30	1.35	1.37	1.42
4	$d_{N(CO)\cdots H}$			1.83	1.69	1.41	1.02
5	$d_{N_{endo}\cdots H}$	1.00		1.02	1.05	1.25	1.89
6	$d_{C2\cdots N_{endo}}$	1.45		1.42	1.37	1.35	1.32
7	$d_{C2\cdots N_{exo}}$	1.29		1.31	1.36	1.38	1.42
8	$d_{N_{endo}\cdots N(CO)}$			2.69	2.51	2.50	2.68

The energetics of the stepwise reactions of tautomers **51b** and **53b** with MeNCO have been calculated and two TSs and one dipolar intermediate have to be considered in each case (Tables 8 and 9, entry 1). The intrinsic reaction coordinate (IRC)[34] calculations demonstrate in both cases that **TS1** and **TS2** connect the reactant and the products with the dipolar intermediate (**I**).

Figures 1 and 2 displays the optimized geometries for the four transition structures and the two intermediates for endo and exo stepwise pathways. In both cases, the process occurs after the initial nucleophilic attack of the azomethine nitrogen to the isocyanate group leading to relatively early transition states on the reaction coordinates (Tables 8 and 9, entry 2).

Dihedral angles collected in Table 10 represent a strong evidence supporting the quasi-planar geometries of **TS1**, **TS2**, and the intermediate **I** for both endo and exo processes. The frontal approach of thiazoline to the isocyanate is a consequence of the nuclephilic attack of the unshared pair of the sp^2-hybridized nitrogen atom.

(33) (a) Bosc, J. J.; Forfar, I.; Jarry, C.; Ouhabi, J.; Leger, J. M.; Carpy, A. *Arch. Pharm. (Weinheim)* **1990**, *323*, 561−566. (b) Jarry, C.; Forfar, I.; Thomas, J.; Leger, J. M.; Laguerre, M. *Heterocycles* **1993**, *36*, 2465−2473.

(34) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368. (b) Head-Gordon, M.; Pople, J. A. *J. Chem. Phys.* **1988**, *89*, 5777−5786.

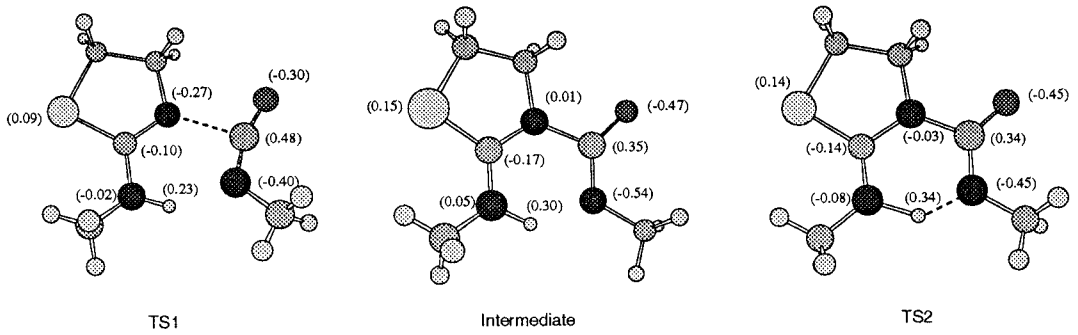


Figure 1. Atomic charges of transition structures and intermediate for endo adduct process.

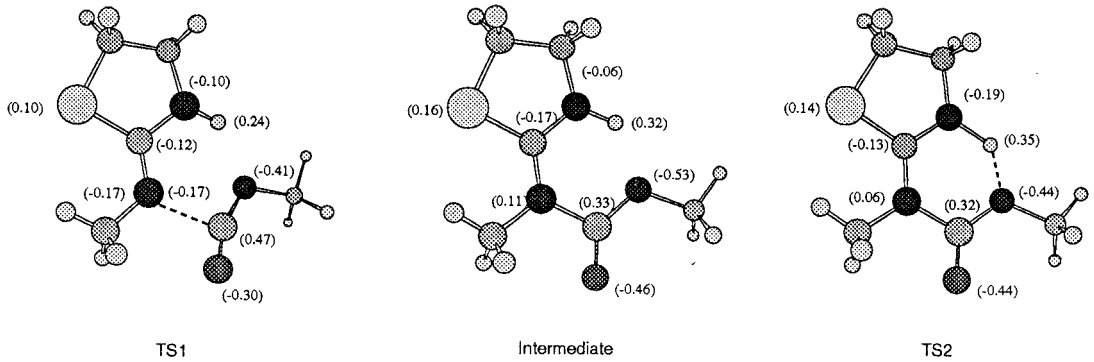


Figure 2. Atomic charges of transition structures and intermediate for exo adduct process.

Table 10. Dihedral Angles (Deg) of TSs and Intermediates for the Endo and Exo Adduct Processes

	endo				exo		
angle	**TS1**	**I**	**TS2**	angle	**TS1**	**I**	**TS2**
N(CO)−C(O)−N_{endo}−C2	−2.7	1.2	−14.8	N(CO)−C(O)−N_{exo}−C2	−18.6	0.0	−10.4
C(O)−N_{endo}−C2−N_{exo}	−12.4	−2.0	−10.8	C(O)−N_{exo}−C2−N_{endo}	−11.0	0.0	5.8
N_{endo}−C2−N_{exo}−H	15.7	1.8	−4.0	N_{exo}−C2−N_{endo}−H	25.5	0.0	−1.4
C2−N_{exo}−H−C(O)	2.7	0.5	−1.0	C2−N_{endo}−H−C(O)	6.0	0.0	−1.0

This situation contrasts with the well-known "two-plane orientation complex" which precedes the bond-forming and bond-breaking processes of a pericyclic reaction.

Both TSs also feature close N−C bond lengths (2.06 and 2.09 Å), thereby suggesting a similar nucleophilic character at the azomethine nitrogen atoms. Likewise, the isocyanate moiety remains practically unaffected in both TSs as evidenced by the bond angle N−C−O of about 160° (the bond angle N−C−O at the methyl isocyanate is 168.3°).

Nevertheless, in the intermediates where the N−C bond is almost completely formed (1.52−1.54 Å), the carbonyl carbon of the isocyanate possesses a trigonal geometry. A key structural feature of intermediates and TSs is the hydrogen bonding interaction between the nitrogen atoms of both fragments. The intramolecular bond distances $N_{endo(exo)}\cdots N(CO)$ are predicted to be ≤2.72 Å (Tables 8 and 9, entry 8), in agreement with the values found for **10** and **15a** by X-ray analyses.

The reaction does not stop after the nucleophilic attack: proton transfer occurs in the second step. When the transition state is reached the NH···N distances are 1.25 and ∼1.42 Å for each structure. The bond angle N−H−N (∼134°) is compatible with an almost planar transition state (Table 10).

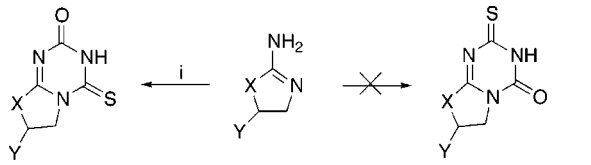
The progression of bond lengths C−N → C═N and C═N → C−N at the stationary points through the reaction coordinate (Tables 8 and 9, entries 6 and 7) does reflect the structural variation experienced by 2-methyl-amino-2-thiazoline or its tautomer during the addition reaction.

The endo addition exhibits two energetic barriers of 10.1 and 3.8 kcal mol^{-1}, respectively, to afford **42b** in a slightly exothermic process (22.2 kcal mol^{-1}). It should be noted the relatively low energy barriers assuming that the transformation occurs with charge separation. Nevertheless, both the positive and negative charges at the dipolar zwitterion are largely delocalized through their neighboring atoms. Concerning the exo addition, yielding **45b**, the process is less exothermic as well (∼17.9 kcal mol^{-1}) via two close activation barriers of 11.8 and 3.9 kcal mol^{-1}. Again, the endo approach is both kinetic and thermodynamically favored.

Concluding Remarks

The preceding results constitute an in-depth exploration on the reactivity of 2-amino-2-thiazolines toward isocyanates and isothiocyanates and the rearrangement of the resulting adducts. The endo regiospecificity observed appears to be a general and unifying rule for these five-membered heterocycles having two nonequivalent amidine-type nitrogen atoms, which enables selective functionalizations. Additional and interesting examples also illustrate this tendency in other heterocyclic systems, even with aromatic character. Thus, 2-hydrazino-2-thiazoles (**55**) react with isocyanates to give the derivatives **56**, in which the attack occurs at the exocyclic NH group.[35] This is however consistent with an attack at the

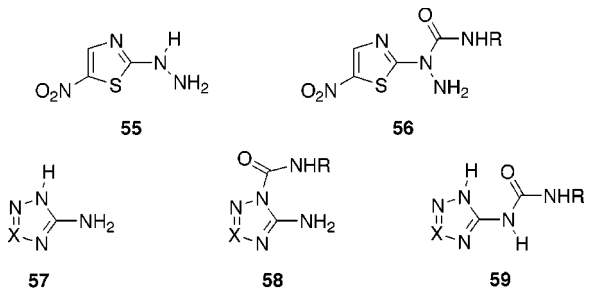
Scheme 8[a]



60 X=S, Y = H **6** X=S, Y = H **61** X=S, Y = H
63 X=O, Y = CH_2R **62** X=O, Y = CH_2R **64** X=O, Y = CH_2R

[a] Reagents: (i) ClCONCS or EtOCONCS.

more nucleophilic endo nitrogen atom followed by subsequent rearrangement to the exocyclic position of an unsubstituted 2-aminoheterocycle. Similarly, 3-amino-1,2,4-triazoles (**57**, X = CH)[36] or 5-amino-1,2,3,4-tetrazoles (**57**, X = N)[37] react with iso(thio)cyanates and alkylating agents[38] at a ring nitrogen to give endo adducts (**58**) that underwent rearrangement to **59** on raising the temperature.



55 **56**

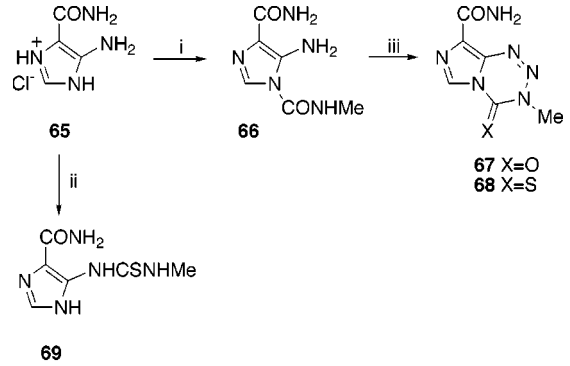
57 **58** **59**

Not only 2-amino-2-thiazoline[7g,39] but also 2-amino-2-selenazoline,[7g] 2-amino-5,6-dihydro-4*H*-1,3-thiazine,[7g] and 2-amino-2-oxazolines (**62**)[33b] react with the highly reactive ethoxycarbonyl isothiocyanate to give exclusively adducts resulting from an endo addition (**60** or **63**). However, the reaction with benzoyl isothiocyanate produces a mixture of endo and exo adducts (Scheme 8).[7h]

Remarkably, a recent synthesis of the antitumor drug Temozolomide (**67**)[40] clearly illustrates the differential reactivity of endo and exo positions toward heterocumulenes (Scheme 9). The key step in this synthesis is the reaction of **65** with methyl isocyanate, which gives selectively the ureido precursor **66**. However, the thio-analogue, thiotemozolomide (**68**), could not be obtained as the condensation of **65** with methyl isothiocyanate took place at the exo position, presumably by an in situ rearrangement of the endo adduct, affording **69**.

In summary, the present study provides a reasonable interpretation of this type of reactivity and outlines some mechanistic considerations. Moreover, this survey

Scheme 9[a]



65 **66** **67** X=O **68** X=S

69

[a] Reagents: (i) MeCNO, Me_2SO or MeCN, 0−25 °C, NEt_3; (ii) MeNCS; (iii) $NaNO_2$, 2 M HCl, rt.

clarifies the misassignment of structures attributed to numerous isomers in the past, particularly those with biological properties. Thus, it is well-known that isocyanates and isothiocyanates are powerful carbamoylating and thiocarbamoylating agents and their interaction with amino groups of macromolecules are relevant in understanding the process of carcinogenesis and its clinical treatment.[41]

Experimental Section

General Methods. All melting points were determined on a capillary apparatus and are uncorrected. Solid-state IR spectra were recorded in KBr pellets and oily samples as obtained. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively. Chemical shifts were reported in ppm (δ) using Me_4Si as internal standard. The multiplicity of ^{13}C NMR spectra was determined by DEPT measurements. FAB mass spectrometry was performed using Xe (and/or Ar) atoms having a kinetic energy equivalent to 7 kV at an accelerating voltage of 4 kV. Determinations were made by adding sodium ions in the form of sodium iodide; and glycerol, 1-thioglycerol, and 3-nitrobenzyl alcohol were used as the matrix solution. Analytical TLC was developed on precoated plates with silica gel Merck 60 GF_{254} of 2 mm thickness. Elemental analyses were performed by the Servicio de Microanálisis, Universidad de Extremadura. Reagents were purchased from commercial suppliers or prepared by literature methods. **CAUTION:** *2-chloroethyl isothiocyanate[18a] is a potential carcinogenic agent and should be handled with extreme care. All reactions involving isocyanates and isothiocyanates should be conducted in a well-ventilated hood.*

Computational Methods. Semiempirical calculations on reactants, transition structures, and reaction products were performed using the PM3[29] method from the Gaussian 94 package of programs.[42] All stationary points were located on the potential energy surfaces and characterized by frequency calculations according to the number of negative vibrational frequencies.[43] The corresponding geometries were subsequently refined by minimizing the energy with full optimiza-

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tion of all geometric variables (bond lengths, bond angles, and dihedral angles).

General Preparation of (*Z*)-2-Alkyl(aryl)imino-*N*-alkyl-(aryl)thiazolidinecarbothioamides (14a−d). To a solution of the corresponding 2-alkyl- or 2-phenyliminothiazolidine hydrochlorides (**13a**−**c**, 1.0 mmol)[15] in pyridine (2 mL) was added the alkyl(aryl) isothiocyanate (1.0 mmol), and the reaction mixture was kept at room temperature for 24 h. Then, it was poured into ice−water and extracted with CH_2Cl_2. The combined organic extracts were washed with 3 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate, and water, dried over anhydrous $MgSO_4$, and evaporated to give the title compounds as homogeneous oils or crystals.

(*Z*)-2-Phenylimino-*N*-(4-tolyl)-3-thiazolidinecarbothioamide (14a): 80% yield from **13a** and 4-MeC_6H_4NCS; mp 119−121 °C; IR (KBr) 3000−2700, 1600, 1540, 815, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.90 (s, 1H), 7.42−6.97 (m, 9H), 4.90 (t, J = 7.0 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.2, 159.0, 148.4, 136.3, 136.1, 129.4, 129.3, 125.2, 125.1, 121.3, 54.9, 24.8, 21.1. Anal. Calcd for $C_{17}H_{17}N_3S_2$: C, 62.32; H, 5.23; N, 12.83. Found: C, 62.45; H, 5.41; N, 12.67.

(*Z*)-2-Phenylimino-*N*-methyl-3-thiazolidinecarbothioamide (14b): 73% yield from **13a** and MeNCS; mp 116−117 °C; IR (KBr) 3000−2800, 1600, 1550, 770, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.02 (bs, 1H), 7.39−6.92 (m, 5H), 4.83 (t, J = 7.0 Hz, 2H), 3.19 (d, J = 4.6 Hz, 3H), 3.12 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 177.8, 158.7, 129.0, 123.3, 120.8, 54.9, 32.2, 25.1. Anal. Calcd for $C_{11}H_{13}N_3S_2$: C, 52.56; H, 5.27; N, 16.11. Found: C, 51.78; H, 5.46; N, 16.02.

(*Z*)-2-[(2,2-Dimethoxy)ethyl]imino-*N*-methyl-3-thiazolidinecarbothioamide (14c): 52% yield from **13b** and MeNCS; mp 94−95 °C; IR (KBr) 3120, 3000−2800, 1620, 1555, 1370, 1290, 1250, 1190, 1135, 1085, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.31 (bs, 1H), 4.75 (t, J = 7.0 Hz, 2H), 4.57 (t, J = 5.5 Hz, 2H), 3.40 (s, 6H), 3.38 (d, J = 5.5 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 3.13 (d, J = 4.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 158.6, 103.2, 56.2, 54.2, 53.6, 32.0, 25.2. Anal. Calcd for $C_9H_{17}N_3O_2S_2$: C, 41.04; H, 6.51; N, 15.95. Found: C, 40.98; H, 6.49; N, 15.96.

(*Z*)-*N*-Methyl-2-(1-propyl)imino-3-thiazolidinecarbothioamide (14d): 45% yield from **13c** and MeNCS; oil; IR (neat) 3120, 3000−2800, 1610, 1545, 1440, 1420, 1355, 1320, 1275, 1230, 850, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.50 (bs, 1H), 4.72 (t, J = 7.0 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H), 3.14 (t, J = 7.0 Hz, 2H), 3.13 (d, J = 4.4 Hz, 3H), 1.65 (m, J = 7.1 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.8, 156.7, 56.8, 53.9, 31.8, 25.1, 23.8, 11.8. Anal. Calcd for $C_8H_{15}N_3S_2$: C, 62.70; H, 9.86; N, 27.42. Found: C, 62.52; H, 9.56; N, 27.69.

General Preparation of (*Z*)-2-Alkyl(aryl)imino-*N*-alkyl-(aryl)-3-thiazolidinecarboxamides (15a−e). To a solution of the corresponding 2-alkyl or 2-phenyliminothiazolidine hydrochlorides (**13a**−**c**, 1.0 mmol)[15] in pyridine (2 mL), the alkyl(aryl) isocyanate (1.0 mmol) was added and the reaction mixture was kept at room temperature for 24 h. Then, it was poured into ice−water and the resulting solid filtered, washed with cold water, and recrystallized from 96% aqueous ethanol.

(*Z*)-2-Phenylimino-*N*-(3-methoxyphenyl)-3-thiazolidinecarboxamide (15a): 76% yield from **13a** and 3-$MeOC_6H_4$-NCO; mp 135−136 °C; IR (KBr) 3080−2900, 2820, 1690, 1615, 1590, 1560, 1290, 1280, 1230, 1210, 1050, 860, 765, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.01 (bs, 1H), 7.42−6−61 (m, 9H), 4.38 (t, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.17 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 160.1, 158.4, 150.8, 149.1, 139.3, 129.5, 129.2, 124.9, 121.5, 112.3, 109.6, 105.5, 55.3, 48.9, 25.6. Anal. Calcd for $C_{17}H_{17}N_3O_2S_2$: C, 62.37; H, 5.23; N, 12.83. Found: C, 61.99; H, 5.28; N, 12.75.

(*Z*)-2-Phenylimino-*N*-(4-tolyl)-3-thiazolidinecarboxamide (15b): 70% yield from **13a** and 4-MeC_6H_4NCO; mp 129−131 °C; IR (KBr) 3060−2800, 1685, 1610, 1600, 1580, 1550, 1280, 1230, 1190, 810, 760, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.87 (bs, 1H), 7.41−6−99 (m, 9H), 4.38 (t, J = 7.1 Hz, 2H), 3.15 (t, J = 7.1 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 150.9, 149.2, 135.4, 133.2, 129.4, 129.2, 124.8, 121.5, 120.0, 48.9, 25.7, 20.8. Anal. Calcd for $C_{17}H_{16}N_3OS$: C, 65.78; H, 5.19; N, 13.50. Found: C, 65.52; H, 5.44; N, 13.21.

(*Z*)-2-Phenylimino-*N*-methyl-3-thiazolidinecarboxamide (15c): 70% yield from **13a** and MeNCO; mp 129−131 °C; IR (KBr) 3080, 3000−2800, 1600, 1585, 1535, 760, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.40 (bs, 1H), 7.38−6−91 (m, 5H), 4.29 (t, J = 7.0 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H), 2.89 (d, J = 4.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.0, 154.2, 149.7, 129.1, 124.5, 121.3, 48.9, 26.5, 25.8. Anal. Calcd for $C_{11}H_{13}N_3OS$: C, 56.14; H, 5.56; N, 17.85. Found: C, 56.25; H, 5.36; N, 17.47.

(*Z*)-2-[(2,2-Dimethoxy)ethyl]imino-*N*-phenyl-3-thiazolidinecarboxamide (15d): 86% yield from **13b** and PhNCO; mp 63−64 °C; IR (KBr) 3080−2840, 1685, 1635, 1600, 1560, 1500, 1450, 1360, 1300, 1185, 1075, 960, 745, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.31 (bs, 1H), 7.52−7.04 (m, 5H), 4.66 (t, J = 5.6 Hz, 1H), 4.29 (t, J = 7.0 Hz, 2H), 3.45 (d, J = 5.6 Hz, 2H), 3.43 (s, 6H), 3.20 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 158.1, 151.1, 138.5, 128.9, 123.2, 119.5, 103.2, 55.6, 53.4, 48.3, 25.9. Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19; N, 13.58. Found: C, 54.00; H, 6.27; N, 13.32.

(*Z*)-*N*-Phenyl-2-(1-propyl)imino-3-thiazolidinecarboxamide (15e): 60% yield from **13c** and PhNCO; mp 65−67 °C; IR (KBr) 3080−2800, 1690, 1635, 1600, 1565, 1500, 1450, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.41 (bs, 1H), 7.49−7.04 (m, 5H), 4.25 (t, J = 7.0 Hz, 2H), 3.24 (t, J = 6.8 Hz, 2H), 3.17 (t, J = 7.0 Hz, 2H), 1.73 (m, J = 6.9, 6.8 Hz, 2H), 1.04 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1, 151.3, 138.5, 128.8, 123.1, 119.6, 56.7, 48.0, 25.7, 24.2, 12.1. Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.28; H, 6.51; N, 15.95. Found: C, 59.27; H, 6.53; N, 15.81.

Isomerization Experiments. Method A. A flask charged with pure *endo* adduct (0.5 mmol) was heated until complete melting and held there for 5 min. The flask was removed from the oil bath, and the melt was extracted into $CDCl_3$ and analyzed by NMR spectroscopy.

Method B. A solution of the endo adduct (0.5 mmol) was refluxed in benzene (3.0 mL) for 24 h. The reaction mixture was cooled to room temperature, the solvent evaporated, and the residue dissolved in $CDCl_3$ and immediately monitored by NMR spectroscopy.

Trapping Experiments. An equimolar mixture of endo adduct (0.5 mmol) and an appropriate isocyanate or isothiocyanate (0.5 mmol) in benzene (5.0 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature, the benzene evaporated, and the residue dissolved in $CDCl_3$ and characterized by NMR spectrometry.

Reaction of *N*,*N*′-Diphenylurea with 2-Chloroethyl Isothiocyanate. To a suspension of NaH (60% dispersion in mineral oil, 3.0 mmol) in dry THF (10 mL) was added dropwise a solution of *N*,*N*′-diphenylurea (0.42 g, 2.0 mmol) in dry THF (30 mL), and the reaction mixture was stirred at 0 °C (external bath) for 1 h. Then, 2-chloroethyl isothiocyanate (0.3 mL, 3.0 mmol) was added and the stirring slurry was allowed to warm to room temperature. After 1 h, it was diluted with brine (30 mL), the ethereal layer separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated to give **12** (0.3 g, 44%).

NMR Monitoring in THF-d_8. To a suspension of NaH (60% dispersion in mineral oil, 0.2 mmol) in THF-d_8 (0.5 mL) was added *N*,*N*′-diphenylurea (0.02 g, 0.09 mmol) in THF-d_8 (0.5 mL), and the reaction mixture was kept at −20 °C for 24 h. Then, it was filtered, and cold (−20 °C) 2-chloroethyl isothiocyanate was added (13 μL, 0.14 mmol). NMR spectra were recorded at 15-min intervals from −20 to +20 °C.

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Supporting Information Available: X-ray acquisition data, Figures S1 and S2, and Tables S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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