Synthetic and Theoretical Aspects of New Dimroth Rearrangement of 6-Aminopyran-2-ones to 6-Hydroxypyridin-2-ones via Carbamoyl Ketenes

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Two alternative directions for thermal transformation of 6-amino-4-oxopyrano[3,4-*d*] [1,2,3]thiadiazoles **1**, leading either to 6-hydroxy-4-oxo-[1,2,3]thiadiazolo[4,5-*c*]pyridines **2** or 2-cyano-2-(1,2,3-thiadiazol-5-yl)acetamide **4b**, were observed. The first one represents a new, Dimroth-type rearrangement and proceeds by thermal opening of the pyrane ring, followed by the simultaneous rotational isomerization of the ketene intermediate **7** (*s-cis*) to **7** (*s-trans*) and its recyclization onto the amido group to form the pyridin-2-one cycle. The first step of the rearrangement has a calculated [B3LYP/6-31G(d)] activation barrier of 24–34 kcal/mol, the involvement of amines reduces it by ca. 5 kcal/mol [PCM-B3LYP/6-31G(d), DMSO]. In contrast, the recyclization step onto the amido group is calculated to occur essentially barrierless ($\Delta E < 2$ kcal/mol). The influence of substituents, in particular of those capable of intramolecular hydrogen bonding, on the preferred reaction path was also studied. The alternative ring opening of the pyrane cycle was calculated to be at least 5 kcal/mol [B3LYP/6-31G(d)] less favorable than the Dimroth rearrangement.

Introduction

The processes of the interchange of exo- and endocyclic heteroatoms belong to the family of Dimroth rearrangements.[1] These reactions are widespread in the chemistry of five- and six-membered heterocyclic compounds[2] and represent a useful synthetic methodology to obtain a variety of ring systems. Recently, a new synthetic approach to heterocyclic compounds based on the knowledge of rearrangements and complex ring transformations was formulated in our laboratory.[3] Although many six-membered heterocyclic compounds, including pyridines, pyrimidines, oxazines, thiapyranes are able to undergo the rearrangements, to the best of our knowledge, there are no data on the rearrangement in the pyrane series so far.

Apart from the synthetic value, rearrangements of heterocyclic compounds represent a convenient method to generate and study very reactive intermediates.[4] In fact, the reversible intramolecular cyclization of reactive groups onto alternative nucleophilic centers is a common feature of a rearrangement. To elucidate the features of the rearrangements discovered in our laboratory in the series of 1,2,3-thiadiazoles, 1,2,3-triazoles and 1,2,3-thiadiazines[4–6] we have studied the cyclizations of 2-diazothioacetamides and 2-diazoamidines by experimental and theoretical methods.[4,5]

Based on previous knowledge of the mechanisms of electrocyclic reactions of ketenes[7–19] and on known facts of their formation from pyran-2-ones[20–25] we anticipated 6-aminopyran-2-ones to be good precursors for the generation of carbamoylketene intermediates that can recyclize by interaction of the ketene moiety with the nitrogen atom of the amido group to form the isomeric 6-hydroxypyridin-2-ones.

In the following we describe our findings concerning new rearrangements in the series of pyranones. The experimental results and mechanistic details of these reactions are interpreted with the aid of quantum chemical (density functional theory[26]) calculations.

Results and Discussion

Experimental Results

The synthesis of 6-amino-4-oxopyrano[3,4-*d*][1,2,3]thiadiazoles has been recently published.[27,28] Now we have found that heating of pyranones **1a**,**c**–**e** with either $N(C_2H_5)_3$ or pyridine in DMF solution at 120 °C leads to isomeric 4-oxo[1,2,3]thiadiazolo[4,5-*c*]pyridines **2a**,**d**,**e** (Scheme 1). Isolation of **2c** by acidification of **2c′** (final transformation in Scheme 1) was unsuccessful (see Exp. Sect. for details).

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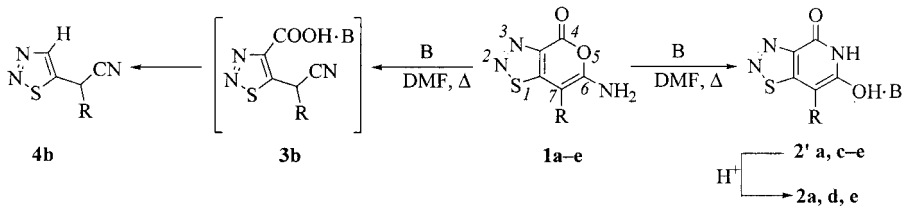


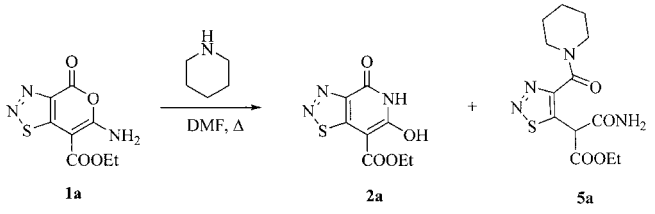
R=COOEt (a), CONHMe (b), CN (c), COOMe (d), $COOCD_3$ (e)

Scheme 1.

The net result of this new rearrangement is the interchange of the ring oxygen atom with the nitrogen atom of the amino group. The structure of products **2a**,**c**–**e** was proved by IR, ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry. The most significant indication for the pyranone → pyridone rearrangement is the absence of the lactone carbonyl valence stretching band at 1760 cm^{-1} that is typical for the pyranone ring.[28] Instead, all products showed IR bands at 1650–1680, characteristic for the lactam moiety. The C-6 signal in the ^{13}C NMR spectra of pyridones **2** (δ = 156–157 ppm) is shifted upfield compared to the C-6 signal in pyranones **1** (δ = 164–165 ppm) which is also consistent with the proposed structure.

The structure of **2a** was finally proved by comparison with an authentic sample of this compound independently prepared by another method.[27] In contrast to pyranone **1a,** under similar reaction conditions *N*-methylcarboxamide **1b** led to cyanoacetamide **4b** in very poor yield together with mostly tar (Scheme 1). The formation of this compound can be rationalized by an alternative ring opening – breaking of the O-5–C-6 rather than the O-5–C-4 bond of the pyranone ring – to 1,2,3-thiadiazole-4-carboxylic acid derivative **3b** that in turn, like other 1,2,3-thiadiazole-4-carboxylic acids,[5] undergoes decarboxylation to give the final product **4b.**

The rearrangement of pyranones **1** to pyridinones **2** can also be accomplished under mild reaction conditions. For instance, heating of **1a** with morpholine or piperidine affords the product of rearrangement **2a** exclusively in the reaction with morpholine, and as major product in the reaction with piperidine.[28] In this latter reaction, piperidineamide **5a** as minor product is also formed (Scheme 2).



Scheme 2.

It is interesting to note that the reaction of compound **1a** with primary amines proceeds generally by the attack on the pyranone carbonyl group (similar to the formation of compound **5a**) followed by intramolecular cyclization to give N^5-substituted 6-hydroxy-4-oxo-[1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxamides.[28] In contrast, the reaction of **1b** with methylamine results mostly in the formation of carboxylate **3b** – the precursor of **4b** – which immediately cyclizes into initial pyranone **1b** upon acidification.[28] Consequently, the reaction pathway is strongly influenced by the nature of the substituent in position 7 of the heterocyclic system and by the nature of the amine.

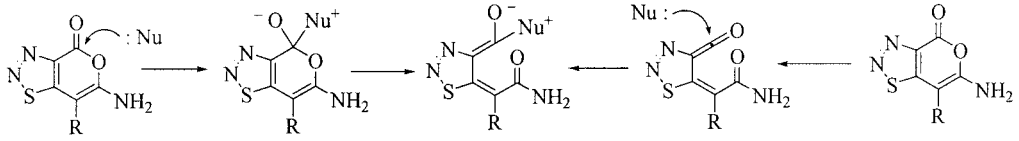
Although the mechanism of the Dimroth rearrangement is seemingly quite clear, that of the discovered transformation of pyranones **1** in the presence of tertiary and secondary amines could not be completely rationalized thereby.

The thermal ring opening of pyran-2-ones without support of a nucleophile is a common reaction.[20–25] Such thermal ring openings of the pyran-2-one ring have been shown to occur across a rather low barrier, which was explained by the pseudopericyclic nature of the transition state.[7–19,29] By laser ultraviolet irradiation of α-pyrone,[24] the reverse reaction, i.e. cyclization of the vinylogous α-oxo ketene was shown to be very fast (E_a = 9.4 kcal/mol and log A = 12.4 s^{-1}). Thus, we expect that Dimroth rearrangement of pyranones **1** by a thermally initiated "ring opening/rotation/cyclization" sequence should be possible.

On the other hand the formation of 1,2,3-thiadiazole-4-carboxamides in the reaction of pyranone **1a** with piperidine and primary amines[28] can be rationalised by an initial nucleophilic attack at C-4 prior to ring opening (Scheme 3), which is in line with the accepted mechanism of the Dimroth rearrangement.[30,31]

It was demonstrated earlier[32,33] that reactions between ketenes and nucleophiles, pyridine in particular, take place at extremely low temperatures (15–40 K), to generate ketene–pyridine zwitterions**.** The kinetic monitoring of such reactions revealed that they have extremely low activation enthalpies (approx. 1 kJ/mol) and very large and negative activation entropies (approx. –300 $JK^{-1}mol^{-1}$). Formation of zwitterionic ketene–nucleophile adducts frequently have been postulated and recently confirmed by low-temperature NMR spectroscopy.[34,35] According to calculations, the stability of such zwitterions strongly depends on the solvent polarity.[35] Obviously then, thermal vs. nucleophile-initiated ring opening of pyranones **1** will depend on the nucleophilicity/basicity of the amine used in the respective reaction (Scheme 3).

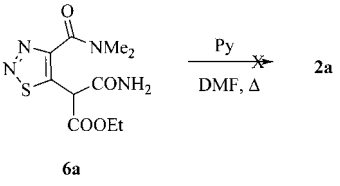
Taking into account these data, we can envisage two general mechanisms for the rearrangement described above. The first one is the nucleophile-assisted ring opening of the



Scheme 3.

pyranone ring followed by recyclization to the pyridone ring by elimination of a molecule of the nucleophile where the nucleophile can either be water or aliphatic amines. The second one is the thermal ring opening of the pyranone to carbamoyl ketenes of type **7a**–**e** with subsequent recyclization onto the nitrogen atom of the amide group to afford the final product **2**.

To shed some light on these two mechanistic alternatives, we have performed the reaction of **1a** in dry and freshly purified DMF under argon where the presence of such nucleophiles, as water and amines can be excluded. Furthermore, we found that the *N*,*N*-dimethylamide of 1,2,3-thiadiazole-4-carboxylic acid **6a** is stable under the usual reaction conditions for rearrangement of pyranones and does not cyclize to pyridone **2a** (Scheme 4).

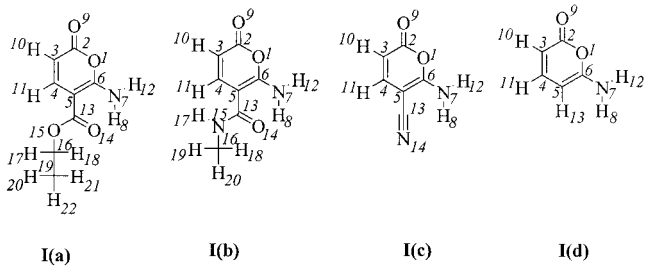


Scheme 4.

Although the first mechanism cannot be completely ruled out by these experiments, they indicate that the rearrangement **1a**,**c**–**e** to **2a**,**c**–**e** by a purely thermally initiated ring opening to and recyclization of ketene intermediates (Scheme 5) is very likely.

The formation of product **4b** and its precursor carboxylic acid **3b** can be explained by an alternative direction for α-pyrone ring opening, viz. breaking of the O-5–C-6 rather than the O-5–C-4 bond. Thus, among the four different substituents (R = COOEt, CONHMe, CN, COOMe and $COOCD_3$), only the amide group induces this alternative pathway.

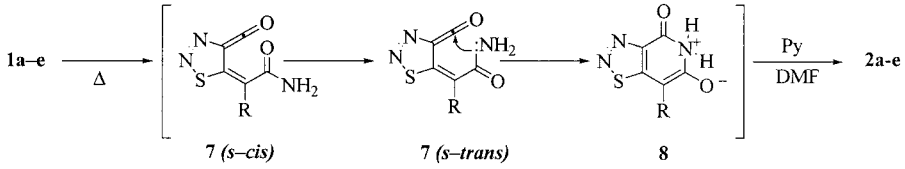
As it was noted in the work of L'abbe,[1] the Dimroth rearrangement in 1,2,3-thiadiazoles is substantially enhanced in the presence of bases. However, it is not clear whether these bases reduce the activation energy of the overall process or simply stabilize the more acidic product of the rearrangement. Although compounds **1a**–**e** contain a masked amide moiety which in general has a low acidity,[36–37] a shift of the protomeric equilibrium induced by the presence of bases prior to rearrangement is also a possibility. To address these questions concerning the mechanistic details of rearrangement reactions shown by pyranones, we carried out quantum chemical (density functional theory[26]) calculations for the rearrangement of 6-amino-4-oxo-pyrano[3,4-*d*][1,2,3]thiadiazoles **1a**–**e**. Because the thiadiazole ring remains unchanged during the reaction and only transformation of the pyranone fragment was observed, the substituted 6-aminopyran-2-ones **I(a**–**d)** were chosen as convenient models for investigation (Scheme 6).



Scheme 6. Numbering of the atoms of **I(a**–**d)**.

Rearrangement of 6-Aminopyran-2-ones I(a–d) to 6-Hydroxypyridin-2-ones IV(a–d) and Formation of Carboxylic Acids VI(a–d) from 6-Hydroxypyran-2-imines V(a–d)

The mechanism of the thermally initiated Dimroth rearrangement is proposed to proceed by the following steps: (i) ring opening of the pyran-2-one moiety to vinylogous α-oxo ketene derivatives, (ii) rotation around the C-5–C-6 bond followed by (iii) recyclization by attack of the amido nitrogen atom to the ketene carbon atom to give the final products. The various stationary structures (minima and transition states) localized for this pathway are shown in Figure 1. Relative energies are summarized in Table 1.



Scheme 5.

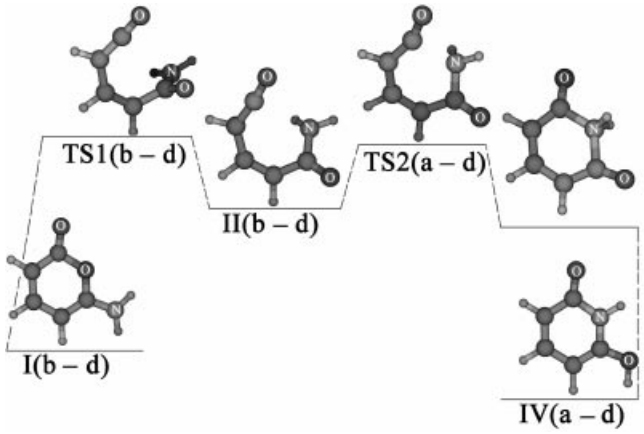


Figure 1. Calculated pathway for thermally initiated rearrangement **I(a–d)** → **IV(a–d)**.

Table 1. Relative energies for rearrangements **I(a–d)** → **IV(a–d)** in kcal/mol.

Structures	B3LYP/6-31G(d)[a]	PCM[b]
I(a)	0.0	0.0
TS2(a)	33.7	28.6
III(a)	29.2	22.7
IV(a)	–8.3	–9.9
I(b)	0.0	0.0
TS1(b)	31.2	24.8
II(b)	23.1	19.9
TS2(b)	24.8	23.2
III(b)	21.6	17.7
IV(b)	–10.1	–12.2
I(c)	0.0	0.0
TS1(c)	26.4	21.0
II(c)	25.3	19.4
TS2(c)	26.4	22.2
III(c)	23.0	16.9
IV(c)	–3.4	–4.6
I(d)	0.0	0.0
TS1(d)	23.7	20.2
II(d)	21.2	18.7
TS2(d)	23.0	23.1
III(d)	19.5	16.5
IV(d)	–3.6	–7.2

[a] With inclusion of ZPE. [b] B3LYP/6-311++G(d,p), DMSO.

It should be noted, that no planar *s-cis* conformation of ketene intermediates could be localized. Instead, the ring opening (stretching of the C-2–O-1 bond) and rotation around the C-5–C-6 bond occurred simultaneously to the *s-trans* intermediate **II(b–d)** [τ(C-4–C-5–C-6–O-1) = 140–150°, see Tables S1–S4 of the Supporting Information (see also the footnote on the first page of this article)]. This failure to localize planar *s-cis* conformations of 5-oxo-2,4-pentadienals **II(a–d)** completely is in line with result obtained by Birney for the cyclization of the parent compound.[11]

Ketene intermediates **II(b,c,d)** with the *s-trans* conformation were obtained to be lower in energy by 1–8 kcal/mol than the corresponding transition states **TS1(b,c,d)** for their formation (see Figure 1 and Table 1). These transition states **TS1(b,c,d)** have a perpendicular arrangement of the vinyl ketene and the amido groups with τ(C-4–C-5–C-6–O-1) ≈ 90°, r(C-2–N-7) = 3.0–3.5 Å, and r(C-2–O-1) = 3.8–3.4 Å (Tables S1–S4 of the Supporting Information).

The overall activation barrier for the ring opening of **I(b)** was calculated to be ca. 5–8 kcal/mol higher than that for **I(c,d)** (Table 1). This substantial difference can be attributed to the extra efforts needed to break the intramolecular hydrogen bond O-14···H-8–N-7 [resonance-assisted hydrogen bond (RAHB)[38–40]] present in **I(b)**. The strength of such intramolecular hydrogen bonds can be estimated by appropriate homodesmotic reactions[41] (Scheme 7, Table 2). This difference in energy was estimated to be 8.1 and 8.3 kcal/mol [B3LYP/6-31G(d)] for **I(a)** and **I(b)**, respectively. Polar solvents are known to substantially reduce the strength of hydrogen bonds.[42] In analogy, by PCM calculations, we find a reduction of the homodesmotic reaction energy $\Delta E_{(A)-(B)}$ by ca. 3–4 kcal/mol in polar solvents for **I(a,b)**. Nevertheless, the reaction barrier is still higher for **I(b)** than either **I(c)** or **I(d)**. The final step, i.e. cyclization of the ketene intermediate **II(b–d)** to **III(b–d)** was calculated to have a rather small activation barrier of < 2 kcal/mol (see Table 1).

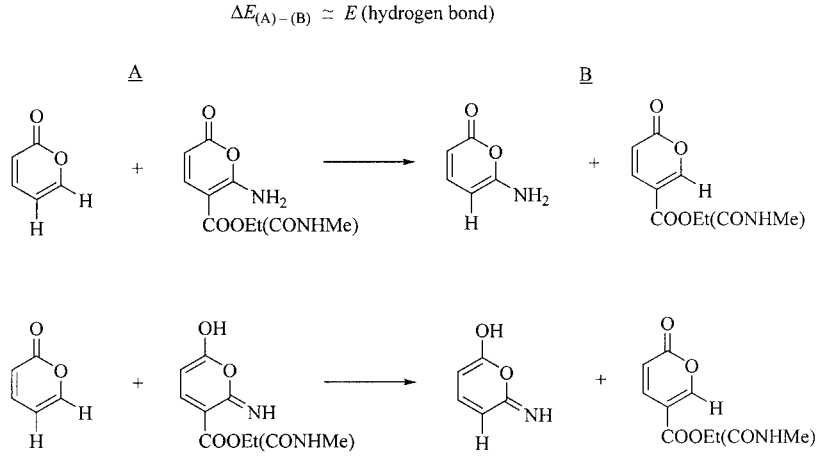
In contrast to **I(b–d)**, the ring opening and cyclization process for ethyl 6-amino-2-oxo-2*H*-pyran-3-carboxylate **I(a)** occurred simultaneously leading directly to zwitterion **III(a)**. No ketene intermediate **II(a)** at all could be obtained. Intrinsic reaction coordinate (IRC) calculations starting from the transition state **TS2(a)** confirmed that pyran-2-one **I(a)** directly is connected to **III(a)** without any intervening intermediate. The barrier of this "ring opening/rotation/cyclization" pathway was found to be ca. 33 kcal/mol, 7–10 kcal/mol higher than **TS2(c)** or **TS2(d)**. As above, the necessity to break the intramolecular hydrogen bond in **I(a)** to form **IV(a)** is the reason of such high a barrier. The presence of two signals for the NH_2 group, δ = 9.63–9.64 and 8.65–8.69 ppm, in the ^{1}H NMR spectra of compounds **1a,d,e** provides some evidence for intramolecular hydrogen bonding.

The overall barrier for the thermal rearrangement **I(a–d)** → **IV(a–d)** was estimated to be ca. 25 kcal/mol for R = H and CN and ca. 32 kcal/mol for R = CONHMe and COOEt.

Moreover, for all three derivatives the barrier for cyclization, ΔE[**TS2(b–d)** – **II(b–d)**] is comparable and, in contrast to the barrier for ring opening, slightly increases in polar solvents (see below).

Transition states for cyclization **TS2(a–d)** were found at r(C-2–N-7) = 2.14–2.18 Å and τ(C-4–C-5–C-6–O-1) = 139–154° (Tables S1–S4 of the Supporting Information). The ketene fragment C-3=C-2=O-9 is considerably bent, α(C-3=C-2=O-9) ≈ 155°. The transition state **TS2(b)** was calculated to be lower than **TS1(b)**, whereas for **I(d,c)** both transition states have similar energies. This difference can be traced back to the presence of an intramolecular resonance-assisted hydrogen bond in **I(b)** to be broken during ring opening.

Zwitterions **III(a–d)** are only 3–4 kcal/mol lower in energy than transition states **TS2(a–d)**; thus, the formation of the zwitterionic intermediates is an endothermic process.



Scheme 7.

Table 2. Reaction energies in kcal/mol for the homodesmotic reactions shown in Scheme 7.

Structure	B3LYP/6-31G(d)[a]	PCM[b]
I(a)	8.1	5.1
I(b)	8.3	4.5
V(b)$_{syn}$	6.5	5.0
V(b)$_{anti}$	0.1	–2.6

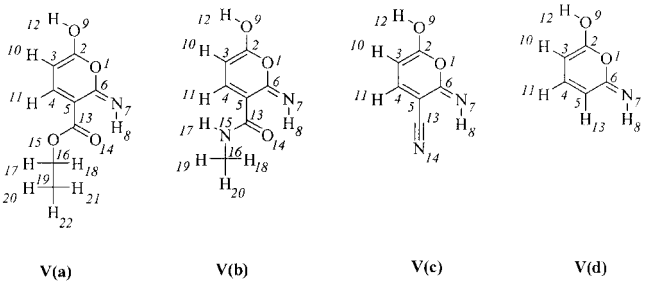
[a] With inclusion of ZPE. [b] B3LYP/6-311++G(d,p), DMSO.

We expect that the proton transfer proceeds with a low activation energy and will not be rate-limiting. As it was shown, the water-assisted prototropic tautomerization of formamide has an activation energy of about 20 kcal/mol at the B3LYP/6-31G** level of theory.[43] Obviously, the deprotonation of $[R_2NH_2]^+$ will proceed with even less efforts than that for lowly acidic amides. Additionally, it was obtained at the MP3/6-311G* level that the proton transfer for $[NH_3–H–NH_3]^+$ system has an activation barrier of ca. 3 kcal/mol.[44] Aromatization of zwitterions by proton transfer finally leads to exothermic formation of 6-hydroxypyridin-2-ones **IV(a–d)**, ΔE_{react} = 3–10 kcal/mol. The largest (most negative) reaction energy was calculated for carboxamide **IV(b)**, the lowest one for carbonitrile **IV(c)**.

To examine the basis-set effect, B3LYP/cc-pVDZ and B3LYP/cc-pVTZ single-point calculations were also carried out (Tables S1–S4 of the Supporting Information). No substantial differences were found thereby for the general picture of the mechanism. The influence of polar solvents on the reaction was modeled by single-point calculations using the polarized continuum model [PCM-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d)].[45–47] Calculations have shown, that the presence of solvent decreases the first activation barrier by 3–7 kcal/mol for 6-aminopyran-2-ones **I(b,c,d)**. As already mentioned above, the second barrier, i.e. ΔE[**TS2(b–d)** – **II(b–d)**], is slightly increased (see Table 1). The exothermicity of the thermal rearrangement was calculated to be larger by 2–3 kcal/mol in dipolar aprotic solvents compared to the gas phase.

Thus, the key step for the Dimroth rearrangement is the ring opening with simultaneous rotation around the C-5–C-6 single bond. In case of R = COOEt and CONHMe, this rotation is accompanied by breaking of the intramolecular hydrogen bond N-7–H-8···O-14 with a concomitant increase of ΔE_{act} for **I(a)** and **I(b)**. The barrier heights of 20–25 kcal/mol in polar aprotic solvents (PCM results in Table 1) are in line with the requirement of heating to accomplish rearrangement of pyrano [3,4-*d*][1,2,3]thiadiazoles **1a–d**.

It is known that lactone ring opening can occur by alternatively breaking either one of the two C–O bonds.[48–49] Such an alternative ring opening can also take place in 6-aminopyran-2-ones **I(a–d)** leading to 5-(1-cyano-1-methylcarbamoylmethyl)-1,2,3-thiadiazole-4-carboxylic acid **3b**. Our preliminary calculations have shown that this process **I(d)** → **VI(d)** has a higher (ca. 72 kcal/mol, Table S8 of the Supporting Information) activation energy than the ring opening via the O-1–C-2 bond. Formally, we can assume that compounds **I(a–d)** due to the presence of an acidic amide group may exist in two (amino and imino) tautomeric forms. Being the heteroanalog of pyran-2-ones **I(a–d)**, imines **V(a–d)** [Scheme 8, for consistency, the same atom numbering for **V(a–d)** is used as for **I(a–d)**] can undergo O-1–C-6 bond breaking/ring opening by a pseudopericyclic mechanism (Figure 2).



Scheme 8. Numbering of atoms of **V(a–d)**.

The calculations have shown that 6-hydroxypyran-2-imines **V(a–d)** are considerably less stable than pyran-2-ones **I(a–d)** (20–30 kcal/mol, Table 3, Charts S4–S7 of the Supporting Information). For **V(b)** two conformers, **V(b)**$_{syn}$,

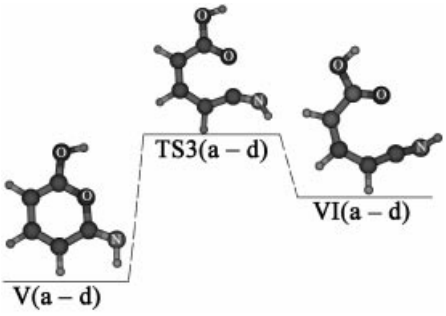


Figure 2. Calculated reaction path for the transformation **V(a–d)** → **VI(a–d)**.

τ(O-1–C-6–N-7–H-8) = 0° and **V(b)**$_{anti}$, τ(O-1–C-6–N-7–H-8) = 179°, are obtained by the calculations. In agreement with the experimentally observed fact, that a homoatomic RAHB N-7···H-17–N-15 is stronger than the heteroatomic O-14···H-8–N-7 one,[38–40] **V(b)**$_{anti}$ is calculated to be less stable by 7 kcal/mol [B3LYP/6-31G(d)] than **V(b)**$_{syn}$. According to the approach of homodesmotic reactions (Scheme 7, Table 2), the strength of hydrogen bonding N-7···H-17–N-15 in **V(b)**$_{syn}$ was calculated to be 6.5 kcal/mol. The bonding O-14···H-8–N-7 in **V(b)**$_{anti}$ was estimated to be negligible, ca. 0.1 kcal/mol, according to the homodesmotic approach. The energy gap $\Delta E_{(A)-(B)}$ was calculated to be even negative within the framework of the PCM model. This result is not unexpected in view of the different character, i.e., no resonance-assisted hydrogen bonding, of the interaction O-14···H-8–N-7 in **V(b)**$_{anti}$.

Table 3. Relative energies for the **V(a–d)** → **VI(a–d)** process.

Process	Differences in energy	B3LYP/6-31G(d)[a]	PCM[b]
V(a)$_{anti}$	$\Delta E_{\mathbf{I(a)–V(a)}anti}$	–33.2	–28.9
→ **VI(a)**	ΔE_{act}	10.3	8.4
	ΔE_{react}	–3.2	–0.5
V(b)$_{anti}$	$\Delta E_{\mathbf{I(b)–V(b)}anti}$	–28.0	–25.3
→ **VI(b)**	ΔE_{act}	16.0	13.7
	ΔE_{react}	9.9	4.4
V(b)$_{syn}$	$\Delta E_{\mathbf{I(b)–V(b)}syn}$	–21.4	–20.1
→ **VI(b)**	ΔE_{act}	14.3	12.6
	ΔE_{react}	12.1	7.3
V(c)$_{anti}$	$\Delta E_{\mathbf{I(c)–V(c)}anti}$	–23.5	–22.3
→ **VI(c)**	ΔE_{act}	16.7	13.7
	ΔE_{react}	10.0	6.0
V(d)$_{anti}$	$\Delta E_{\mathbf{I(d)–V(d)}anti}$	–21.2	–20.7
→ **VI(d)**	ΔE_{act}	15.9	13.9
	ΔE_{react}	6.2	3.3

[a] With inclusion of ZPE. [b] B3LYP/6-311++G(d,p), DMSO.

Relative energies of the transformations **V(a–d)** → **VI(a–d)** are collected in Table 3. Total energies and selected geometrical data are presented in Tables S5–S8 and Charts S4–S7 of the Supporting Information.

Although the 6-hydroxypyran-2-imines **V(a–d)** are less stable than the tautomeric pyran-2-ones **I(a–d)**, the activation barrier for breaking the O-1–C-6 bond is substantially lower than that for the Dimroth rearrangement, i.e. breaking of the O-1–C-2 bond, in **I(a–d)** and was calculated to be 10–17 kcal/mol [B3LYP/6-31G(d), Table 3]. Polar solvents decrease these barriers by ca. 2 kcal/mol (PCM calculation).

The reaction **V(b–d)** → **VI(b–d)** was calculated to be endothermic by 6–10 kcal/mol (see Table 3). Only for **V(a)** → **VI(a)** the process of ring opening was estimated as slightly exothermic [ca. 3 kcal/mol, B3LYP/6-31G(d)].

Combining the energy requirements for tautomerization to the imino forms with the barrier for their ring opening, the overall energy effort for this alternative reaction pathway for model compounds **I(a–d)** is in the range 37–43 kcal/mol, considerably higher than that found for the Dimroth rearrangement (23–33 kcal/mol, Table 1). Interestingly, although the process **V(a)** → **VI(a)** has the lowest activation barrier, the overall energy effort (43.4 kcal/mol) is highest for the rearrangement of **I(a)** by breaking/ring opening of the O-1–C-2 bond. This can be attributed to the low thermodynamic stability of **V(a)**. The tautomer **V(b)**$_{syn}$ is calculated to be ca. 21 kcal/mol higher than **I(b)**. Thus, the overall effort for the alternative ring opening **V(b)**$_{syn}$ → **VI(b)** can be estimated to be 36 kcal/mol, significantly less than for **V(a)** and **V(c)** (8 and 5 kcal/mol, respectively). Given the rather high barrier for the Dimroth rearrangement of **I(b)**, the activation energy for this pathway is just ca. 5 kcal/mol higher. If at all, thus, among the three substituted model derivatives for pyrano[3,4-*d*][1,2,3]thiadiazoles **1a–c**, only the derivative with R = CONHMe **1b** (**Ib**) can be expected to react by breaking of the O-5–C-6 bond (O-1–C-6 bond for the model **Ib**) We take this as evidence to explain the experimentally observed formation of **3b**.

Rearrangement of 6-Aminopyran-2-one Anions [I(a–d)]$^-$ → [IV(a–d)]$^-$ and Alternative Direction of Ring Opening by Breaking of the O-1–C-6 Bond in 6-Aminopyran-2-one Anions [I(b,c)]$^-$

As noted before, the Dimroth rearrangement for thiadiazoles[1] can be accelerated by the presence of nucleophiles. Besides nucleophilic addition to the carbonyl group, ring opening of the formal tetrahedral adduct, rotation and reclosure accompanied by expulsion of the nucleophile, or ketene intermediate stabilization by formation of zwitterionic ketene–nucleophile adducts (Scheme 3), the nucleophile (pyridine in the reactions described here) simply could act as a base resulting in the formation of anions of pyrano[3,4-*d*][1,2,3]thiadiazoles. To check this possibility, calculations have also been carried out for the anions [**I(a–d)**]$^-$ of the model structures (Charts S8–S11 of the Supporting Information). In this case an "in-plane" attack of the imine nitrogen lone pair towards the central ketene carbon atom, expected to occur with particularly low activation energy, is possible.[19] The rearrangement of anions [**I(a–d)**]$^-_{syn}$ was calculated to proceed via a single transition state [**TS4**]$^-$, describing a concerted ring opening by breaking of the O-1–C-2 bond, rotation around the C-5–C-6 bond and, simultaneously, recyclization to the final products [**IV(a–d)**]$^-$. The IRC calculations confirmed that these transition states directly connect the anions of 6-aminopyran-2-ones

[I(a–d)]⁻$_{syn}$ and 6-hydroxypyridin-2-ones **[IV(a–d)]⁻**. Relative energies for this process are collected in Table 4, additional information is also available from Tables S9–S12 and Charts S8–S11 of the Supporting Information.

Table 4. Relative energies for the **[I(a–b)]⁻** → **[IV(a–b)]⁻** process.

Process	Relative energies	B3LYP/6-31G(d)[a]	PCM[b]
[I(a)]⁻ → **[IV(a)]⁻**	ΔE_{act}	45.7	40.8
	ΔE_{react}	–23.4	–21.4
[I(b)]⁻ → **[IV(b)]⁻**	ΔE_{act}	48.0	44.5
	ΔE_{react}	–22.6	–20.7
[I(c)]⁻ → **[IV(c)]⁻**	ΔE_{act}	45.8	41.9
	ΔE_{react}	–22.9	–20.1
[I(d)]⁻→ **[IV(d)]⁻**	ΔE_{act}	43.6	40.4
	ΔE_{react}	–21.8	–21.0

[a] With inclusion of ZPE. [b] B3LYP/6-311++G(d,p), DMSO.

Reaction energies for the anions, ΔE{**[I(a–d)]⁻** → **[IV(a–d)]⁻**}, are substantially more negative (by 15–20 kcal/mol) than for neutral systems; barriers, however, are considerably higher for the anions (by 12–20 kcal/mol, Table 1 and Table 4).

NBO analysis has shown, that the negative charge is largely located on O-9 in **[I(a–d)]⁻** anions and a C-6=N-7 double bond is formed. As a result, the electron-rich –(O-9)⁻ substituent can donate electrons into the σ(O-1–C-2) bond with a concomitant increase of the O-1–C-2 bond order (Table S15 of the Supporting Information). Due to this fact, the activation barrier of the rearrangement by breaking of the O-1–C-2 bond is considerably higher for anions **[I(a–d)]⁻** than for neutral analogues **I(a–d)**. Solvent effects reduce this barrier by almost 5 kcal/mol.

The alternative thermal ring opening along the *r*(O-1–C-6) reaction coordinate in 6-aminopyran-2-one anions **[I(a–d)]⁻** could be localized and completely confirmed by IRC calculations only in two cases, namely for R = CN and CONHMe (Table 5 and Tables S13–S14 and Charts S12–S13 of the Supporting Information).

Table 5. Relative energies for **[I(b,d)]⁻** → **[VII(b,d)]⁻** processes.

Process	Δ*E*	B3LYP/6-31G(d)[a]	PCM[b]
[I(b)]⁻ → **[VII(b)]⁻**	ΔE_{act}	51.2	42.6
	ΔE_{react}	11.9	13.6
[I(c)]⁻→ **[VII(c)]⁻**	ΔE_{act}	45.3	43.1
	ΔE_{react}	8.0	14.4

[a] With inclusion of ZPE. [b] B3LYP/6-311++G(d,p), DMSO.

According to the IRC calculations, transition states **[TS5(b,c)]⁻** directly connect the starting materials, 6-aminopyran-2-ones anions **[I(b,c)]⁻**, with the ring-opened carboxylic acid anions **[VII(b,c)]⁻**. Thus, ring opening and proton transfer of H-12 to the carboxylate oxygen atom O-1 are concerted processes. The reaction **[I(b,c)]⁻** → **[VII(b,c)]⁻** was calculated as endothermic, ΔE_{reac} = 8–12 kcal/mol (Table 5). Protonation of anions **[VII(b,c)]⁻** and formation of neutral 4-cyanobut-2-enoic acid **VI(b,c)** complete the process.

Thus, the formation of anions does not lead to a decrease of the activation barriers of either Dimroth rearrangement or the alternative ring opening by breaking of the O-1–C-6 bond.

Dimroth Rearrangement of 6-Aminopyran-2-one I(d), the Nucleophile-Assisted Mechanism of the Ring Opening of I(d) and Formation of Carboxylic Acid VI(d) from 6-Hydroxypyran-2-imine V(d): Polarizable Continuum Model (PCM) Study

The two most likely pathways of the 6-aminopyran-2-one transformations considered in this paper involve highly polar reaction intermediates and transition states. To estimate the solvent effects precisely, full re-optimization of the stationary points of the **I(d)** → **IV(d)** and **V(d)** → **VI(d)** pathways at the PCM-B3LYP/6-31G(d) level were performed. According to the presented data (Table S16 of the Supporting Information), the change from gas phase to DMSO media led to a greater exothermic effect of the Dimroth rearrangement, by ca. 5 kcal/mol. The geometry of localized stationary points was very close to those obtained at the B3LYP/6-31G(d) level of theory (Tables S4, S8 and S16 of the Supporting Information).

The investigation of the nucleophile-assisted mechanism of the pyrane ring opening was also performed with the polarized continuum model [PCM-B3LYP/6-31G(d)], because the B3LYP/6-31G(d) study has shown that the step of ring opening is the rate-determining step of the rearrangement. The reaction of 6-aminopyran-2-one **I(d)** with the ammonia molecule was taken as a model. Their complex **[I(d)+NH$_3$]** was localized 2 kcal/mol above the non-interacting units at *r*(C-2–N$_{ammonia}$) = 3.554 Å (see Figure 3 and Table S16 of the Supporting Information).

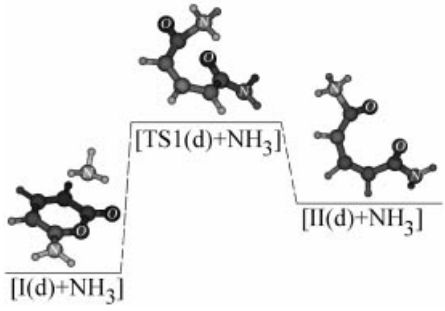


Figure 3. Calculated reaction path for the transformation **[I(d)+NH$_3$]** → **[II(d)+NH$_3$]**.

The pathway corresponding to the approach of the two reagents **I(d)** and **NH$_3$** along this coordinate had no minimum corresponding to the adduct of 6-aminopyran-2-one and ammonia; only the transition state **[TS1(d)+NH$_3$]** was found (Figure 3). According to IRC calculations, **[TS1(d)+NH$_3$]** indeed connects the ketene–amine adduct **[II(d)+NH$_3$]** and the complex **[I(d)+NH$_3$]**. The reaction coordinate *r*(C-2–O-1) in **[TS1(d)+NH$_3$]** was calculated to be 1.856 Å. The *r*(C-2–N$_{ammonia}$) distance was 1.739 Å, considerably longer than the length of the C–N bond in protonated amines RNH_3^+ (1.479 ± 0.005 Å);[50] thus, the C$_{pyran}$–N$_{ammonia}$ bond is not yet formed. The activation

barrier of the ammonia-assisted pyrane ring opening was estimated to be lower than that of the direct ring opening and was ca. 24 kcal/mol [PCM-B3LYP/6-31G(d)]. The adduct of the ketene intermediate with ammonia [**II(d)**+NH_3] was located at *r*(C-2–O-1) = 3.090 Å, 12.9 kcal/mol above complex [**I(d)**+NH_3]. It should be noted, that the *r*(C-2–$N_{ammonia}$) distance was 1.624 Å, which is in agreement with data obtained from experiment and calculations.[51]

Conclusions

Two alternative directions for thermal transformation of 6-amino-4-oxopyrano[3,4-*d*][1,2,3]thiadiazoles **1**, namely to 6-hydroxo-4-oxo[1,2,3]thiadiazolo[4,5-*c*]pyridines **2** and to (1,2,3-thiadiazol-5-yl)cyanoacetamide **4b**, were observed. The first one represents a new, Dimroth-type rearrangement of the aminopyrane series. This rearrangement represents a new and useful tool to construct the pyridine cycle.

Two alternative mechanisms of this new rearrangement were discussed, including both thermal and nucleophile-assisted pyrane ring opening.

According to data obtained from modeling experiments and theoretical investigations, performed with the aid of DFT theory, the mechanism of the observed Dimroth rearrangement consists of a thermal ring opening of the pyrane cycle followed by a simultaneous rotational isomerization of ketene intermediate **7** (*s-cis*) to **7** (*s-trans*) and its recyclization onto the amido group to form the pyridin-2-one system. The ring opening of the pyrane cycle and the simultaneous rotation of ketene intermediate **7** (*s-cis*) to **7** (*s-trans*) was calculated to be the rate-determining step of the rearrangement, ΔE_{act} = 24–34 kcal/mol [B3LYP/6-31G(d)]. The cyclization of ketene **7** (*s-trans*) to form the pyridin-2-one cycle has a rather small calculated activation barrier of < 2 kcal/mol.

It has been shown, that the function of the base reagent consists in a reduction of the activation barrier for the ring opening of the pyrane cycle by ca. 5 kcal/mol [PCM-B3LYP/6-31G(d)] and the stabilization of the final product **2**. We have also shown that the formation of compound **4b** proceeds by breaking of the O-5–C-6 bond of the imino tautomers of compounds **1**, isomerization of the imino ketene moiety to a cyanomethyl group and, finally, of the decarboxylation of acid **3b**.

The data obtained from the B3LYP/6-31G(d) level have shown, that the formation of three-centred hydrogen bonds in compounds **1** hinder the Dimroth rearrangement, but, on the other hand, the formation of a strong three-centred hydrogen bond in 6-hydroxy-2-iminopyranes increases their thermodynamic stability.

Experimental Section

Materials and Methods: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WM-250 and a Bruker DRX-400 in $(CD_3)_2SO$ solutions. Mass spectra were obtained with a Varian MAT 311 machine. Products were analyzed by TLC on DC-Plastikfolien Kieselgel 60 F 254 plates. Melting points were taken in open capillaries and are uncorrected.

4*H*-Pyrano[3,4-*d*][1,2,3]thiadiazoles 1a–e: They were prepared according to a known procedure.[28]

6-Amino-*N*-methyl-4-oxo-4*H*-pyrano[3,4-*d*][1,2,3]thiadiazole-7-carboxamide (1b): Yield 0.42 g from 0.5 g of 5-chloro-1,2,3-thiadiazol-4-carboxylic acid, 61%, m.p. 225 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 2.7 (d, *J* = 5.0 Hz, 3 H, NCH_3), 7.5 (q, *J* = 5.0 Hz, 1 H, CH_3), 8.7 (s, 2 H, NH_2) ppm. MS: *m*/*z* (%) = 226 (53) [M$^+$], 170 (29), 142 (37), 113 (24), 58 (100), 143. IR (KBr): $\tilde{\nu}$ = 3400, 3290, 3165, 1780, 1630, 1550, 1490 cm^{-1}. $C_7H_6N_4O_3S$ (226.21): calcd. C 37.17, H 2.67, N 24.77, S 14.17; found C 37.27, H 2.34, N 24.55, S 14.21.

Methyl 6-Amino-4-oxo-4*H*-pyrano[3,4-*d*][1,2,3]thiadiazole-7-carboxylate (1d): Yield 0.63 g from 0.5 g of 5-chloro-1,2,3-thiadiazol-4-carboxylic acid, 91%, m.p. 225 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 3.87 (s, 1 H, CH_3), 8.69 (s, 1 H, NH), 9.64 (s, 1 H, NH) ppm. MS: *m*/*z* (%) = 227 (100) [M$^+$], 199 (18), 143 (25), 128 (35), 113 (52), 69 (71). IR (KBr): $\tilde{\nu}$ = 3360, 1757, 1676, 1628, 1490, 1290 cm^{-1}. $C_7H_5N_3O_4S$ (227.20): calcd. C 37.01, H 2.22, N 18.49, S 14.11; found C 37.03, H 2.26, N 18.51, S 14.09.

[D$_3$]Methyl 6-Amino-4-oxo-4*H*-pyrano[3,4-*d*][1,2,3]thiadiazole-7-carboxylate (1e): Yield 0.61 g from 0.5 g of 5-chloro-1,2,3-thiadiazol-4-carboxylic acid, 87%, m.p. 237 °C (dec.). ^{1}H NMR ([D$_6$]-DMSO, 400 MHz): δ = 8.69 (s, 1 H, NH), 9.63 (s, 1 H, NH) ppm. MS: *m*/*z* (%) = 230 (100) [M$^+$], 202 (18), 146 (28), 131 (35). IR (KBr): $\tilde{\nu}$ = 1771, 1680, 1622, 1480, 1370 cm^{-1}. $C_7H_2D_3N_3O_4S$ (230.22): calcd. C 37.01, N 18.49; found C 37.04, N 18.53.

Ethyl 6-Hydroxy-4-oxo-4,5-dihydro[1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylate (2a): The starting material **1a** (100 mg) was heated in a mixture of dry DMF (1 mL) and dry pyridine (0.1 mL) at 120 °C for 3 h and then cooled. Intermediate pyridine salt **2a′** was filtered off, suspended in water, treated with 1 N HCl solution to pH ≈ 1 and the product was filtered off, washed with water and dried; yield 70 mg (70%). The sample is completely identical with that synthesized earlier.[27] M.p. 210 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, CH_3), 4.31 (q, *J* = 7.1 Hz, 2 H, OCH_2), 7.5 (s, 2 H, NH + OH) ppm. ^{13}C NMR ([D$_6$]DMSO, 400 MHz): δ = 14.25(CH_3), 65.75 (OCH_2), 85.02 (C-7), 143.98 (C-3a), 155.30 (C-7a), 156.75 (C-6), 161.57(C-4), 167.0 (COOEt) ppm. MS: *m*/*z* (%) = 241 (100) [M$^+$], 195 (38.2), 169 (55.75), 167 (63.17), 141 (25.92), 96 (75.43). IR (KBr): $\tilde{\nu}$ = 3150, 2810, 1690, 1650, 1575, 1470, 1315 cm^{-1}. $C_8H_7N_3O_4S$ (241.23): calcd. C 39.83, H 2.92, N 17.42, S 13.29; found C 39.78, H 2.93, N 17.73, S 13.58.

6-Hydroxy-4-oxo-4,5-dihydro[1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carbonitrile Pyridine Salt (2c′): The salt was obtained as described for **2a′**. The product contained a pyridine moiety even after treatment with HCl due to high basicity. The prolonged heating in acidic media results in hydrolysis of the nitrile function. Yield 90 mg (64%), m.p. 240 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.1 (dd, 2 H, 2 CH), 8.5 (dd, 1 H, CH), 8.9 (d, 2 H, 2 CH), 10.1 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 400 MHz): δ = 66.09 (C-7), 120.29 (CN), 144.77 (C-3a), 157.79 (C-7a), 158.9 (C-6), 162.92 (C-4) + 127.32 (C-3, Pyr), 142.01 (C-2, Pyr), 146.60 (C-4, Pyr) ppm. MS: *m*/*z* (%) = 194 (4) [M$^+$], 168 (2.2), 136 (2.5), 79 (100), 52(60). IR (KBr): $\tilde{\nu}$ = 3160, 3090, 2200, 1660, 1550 1480 cm^{-1}. $C_6H_2N_4O_2S{\cdot}C_5H_5N$ (273.27): calcd. C 48.35, H 2.58, N 25.63, S 11.73; found C 48.37, H 2.60, N 25.67, S 11.76.

Methyl 6-Hydroxy-4-oxo-4,5-dihydro[1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylate (2d): The product was obtained as described for **2a**. Yield 0.12 g from 0.2 g of **1d**, 57%, m.p. 205 °C (dec.). ^{1}H NMR

([D_6]DMSO, 400 MHz): δ = 3.66 (s, 3 H, CH_3), 8.22 (br. s, 1 H, OH), 10.05 (br. s, 1 H, NH) ppm. MS: *m*/*z* (%) = 227 (100) [M^+], 195 (42), 167 (89), 124 (27), 96 (97). IR (KBr): $\tilde{\nu}$ = 1703, 1660, 1480, 1330 cm^{-1}. $C_7H_5N_3O_4S$ (227.20): calcd. C 37.01, H 2.22, N 18.49, S 14.11; found C 37.05, H 2.27, N 18.53, S 14.13.

[D_3]Methyl 6-Hydroxy-4-oxo-4,5-dihydro[1,2,3]thiadiazolo[4,5-*c*]pyridine-7-carboxylate (2e): The product was obtained as described for **2a**. Yield 0.10 g from 0.2 g of **1e**, 50%, m.p. 208 °C (dec.). ^{1}H NMR ([D_6]DMSO, 400 MHz): δ = 8.82 (br. s, 1 H, OH), 10.23 (s, 1 H, NH) ppm. MS: *m*/*z* (%) = 230 (74) [M^+], 195 (29), 167 (64), 124 (19), 57 (100). IR (KBr): $\tilde{\nu}$ = 1690, 1580, 1370 cm^{-1}. $C_7H_2D_3N_3O_4S$ (230.22): calcd. C 37.01, N 18.49; found C 37.06, N 18.52.

2-cyano-*N*-methyl-2-(1,2,3-thiadiazol-5-yl)acetamide (4b): The starting material **1b** (100 mg) was heated in the mixture of dry DMF (1 mL) and dry pyridine (0.1 mL) at 120 °C for 3 h and then cooled. The precipitate was filtered off, washed with water and dried. Yield 16 mg (20%), m.p. 202 °C (dec.). ^{1}H NMR ([D_6]DMSO, 250 MHz): δ = 2.7 (d, 3 H, NMe), 6.0 (br. s, 1 H, CH), 7.2 (m, 1 H, NH), 8.2 (s, 1 H, $CH_{thiadiazole}$). MS: *m*/*z* (%) = 182 (4) [M^+], 154 [$M^+ - N_2$] (10), 125 (7), 97 (72), 58 (100). IR (KBr): $\tilde{\nu}$ = 3950, 2910, 2190, 1573, 1480 cm^{-1}. $C_6H_6N_4OS$ (182.20): calcd. C 39.55, H 3.32, N 30.75; found C 39.58, H 3.36, N 30.79.

Computational Details: All calculations were carried out using the Gaussian98 package.[52] Geometries were completely optimized using Becke's hybrid HF density functional theory method[53] with the Lee–Yang–Parr correlation functional[54] and the 6-31G(d) basis set [B3LYP/6-31G(d)]. The nature of the various critical points was established by performing frequency computations. IRC calculations[55] were also performed for transition-state structures. Additional single-point calculations were performed with the cc-pVTZ basis set[56] (B3LYP/cc-pVTZ). Bulk solvent effects (DMSO solution) were estimated by the polarizable continuum model [PCM,[45–47] B3LYP/6-311++G(d,p) as it was recommended[57]] with single-point calculations. The full-optimization calculation within the PCM model was performed at the B3LYP/6-31G(d) level. The NBO analysis[58] was performed to explore the electronic structure of located stationary points [B3LYP/6-311++G(d,p)].

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