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1,2-DIAZETINES AS USEFUL TOOLS FOR RING TRANSFORMATION REACTIONS WITH ISOTHIOCYANATES – A NEW ENTRY TO 1,3,4-THIADIAZINES

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Abstract – 1,2-Diazetines (**1**) can be acylated with isocyanates (**2**) to give semicyclic urea derivatives (**3**). In contrast, isothiocyanates (**4**) react with **1** under mild conditions to furnish new derivatives of 1,3,4-thiadiazine (**5**). DFT calculations show that two different mechanistic pathways for this ring transformation are possible. N-Acylation is preferred at lower temperatures; whereas an electrocyclic ring opening/cycloaddition process is possible at higher temperatures.

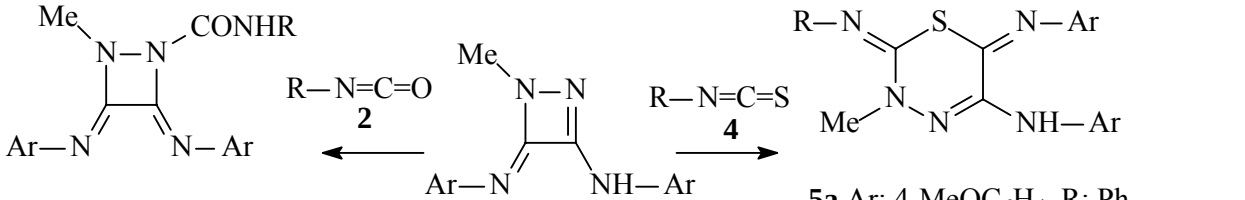
INTRODUCTION

Nitrogen-containing four membered heterocycles are of general interest, not only because of their biological activity but also because they are quite convenient building blocks for other derivatives.[1] They easily react under ring cleavage to undergo facile ring transformation reactions. Although Δ^1-1,2-diazetines

are commonly available, only a very few of their Δ^2-1,2-analogues have been reported in the chemical literature.[2] We have recently succeeded in developing a simple procedure for obtaining such Δ^2-1,2-diazetines of type (**1**); compounds which can also be classified as being cyclic amidrazones of oxalic acid.[3] These heterocycles (**1**) react easily with bases to generate ambidentate anions which can then be alkylated at the ring nitrogen.[3] Continuing with our investigations of these interesting compounds, we now report their acylation reactions with heterocumulenes derived from carbonic acid.

RESULTS AND DISCUSSION

Neither carbon disulfide nor dicyclohexylcarbodiimide react with **1**. However, arylisocyanates (**2**) and their sulfur analogues (**4**) both react under surprisingly mild conditions. Interestingly, they exhibit fundamentally different regioselectivities.



3a Ar = R: 4-MeC_6H_4
3b Ar: 4-$MeOC_6H_4$, R: Ph
3c Ar: 4-MeC_6H_4, R: Ph

5a Ar: 4-$MeOC_6H_4$, R: Ph
5b Ar: 4-MeC_6H_4, R: Et
5c Ar: 4-MeC_6H_4, R: $CH_2CH{=}CH_2$
5d Ar: 4-MeC_6H_4, R: CH_2Ph
5e Ar: 4-MeC_6H_4, R: CH_2COOEt
5f Ar: 4-MeC_6H_4, R: Me

Scheme 1. Reactions of 1,2-diazetines (**1**) with isocyanates (**2**) and isothiocyanates (**4**)

Arylisocyanates (**2**) react smoothly with **1** below room temperature and quite good yields (*ca.* 80%) of yellow crystalline 1:1 adducts (**3a-c**) can be isolated from the reaction mixture. ^{1}H NMR spectra of these adducts show that the N-methyl group undergoes a down-field shift (0.3 ppm) as compared to **1**. An unambiguous structural assignment for **3b** was obtained from single crystal X-Ray analysis which confirmed the formation of a semicyclic urea derivative. The exocyclic 1,4-diaza-1,3-diene functionality takes on an E/Z arrangement. The four-membered ring is, analogous to the dimethyl derivative reported in our earlier study, [3] slightly puckered (torsion angle C1-C2-N1-N2 = 7.6°).

Isothiocyanates (**4**) are much poorer electrophiles than their oxygen analogues (**2**). However, they still react under mild conditions with diazetines (**1**) to give yellow-orange crystals (**5**) (main product) in yields of higher than 80%. These are also formal 1:1 adducts as confirmed by the molecular formula obtained with elemental analyses and MS spectra. Their thermal stability is quite high; in contrast to the derivatives (**3**) which swiftly decompose at *ca.* 100°C, these compounds are stable until their melting points are reached.

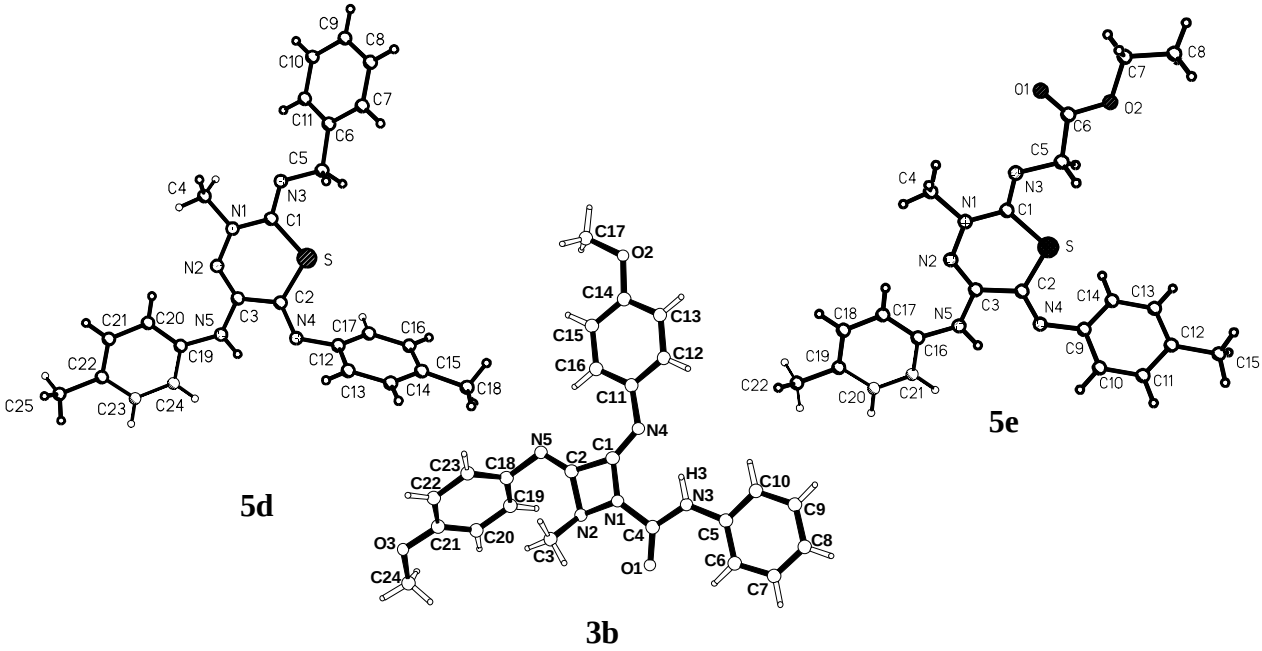
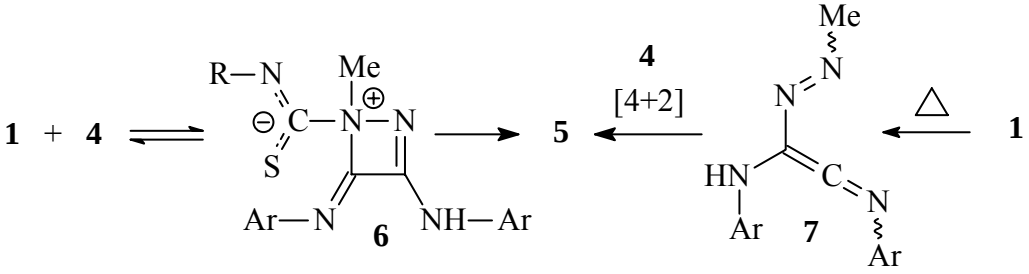


Figure 1. Solid state structures (single crystal X-Ray analyses) of **3b**, **5d** and **5e**; the numbering corresponds to that used for the X-ray analyses. Selected distances [Å] and angles [°]: **3b**: O1 – C4 1.213 (3), N1 – C4 1.395 (3), N1 – C1 1.428 (3), N1 – N2 1.473 (3), N2 – C2 1.440 (3), N3 – C4 1.365 (4), N3 – H3 0.88 (3), N4 – C1 1.262 (3), N5 – C2 1.249 (4), C1 – C2 1.524 (4), C4 – N1 –N2 120.7 (2), C1 – N1 – N2 92.6 (2); **5d**: S – C(1) 1.773 (2), S – C(2) 1.757 (2), C(2) – C(3) 1.480 (3), C(2) – N(4) 1.269 (3), C(3) – N(2) 1.289 (3), C(3) – N(5) 1.380 (3), N(1) – N(2) 1.370 (2), C(1) – N(1) 1.376 (3), C(1) – N(3) 1.275 (3), C(2) – S – C(1) 104.15 (10), N(2) – N(1) – C(1) 128.35 (18), C(3) – N(2) – N(1) 122.40 (18), N(1) – C(1) – S 119.40 (15), C(3) – C(2) – S 117.87 (15), N(2) – C(3) – C(2) 127.58 (19); **5e**: S – C(1) 1.777 (2), S – C(2) 1.759 (2), C(2) – C(3) 1.481 (3), C(2) – N(4) 1.273 (3), C(3) – N(2) 1.292 (3), C(3) – N(5) 1.379 (3), N(1) – N(2) 1.371 (2), C(1) – N(1) 1.368 (3), C(1) – N(3) 1.277 (3), C(2) – S – C(1) 105.09 (10), N(2) – N(1) – C(1) 128.19 (18), C(3) – N(2) – N(1) 122.98 (18), N(1) – C(1) – S 118.94 (16), C(3) – C(2) – S 117.05 (15), N(2) – C(3) – C(2) 127.52 (19).

Single crystal X-Ray analysis of **5d** and **5e** identified them as six-membered NS heterocycles of 1,3,4-thiadiazine type (Figure 1). Instead of the typical acylation found for the arylisocyanates (**2**), the NCS functionality had reacted *via* a complicated ring transformation reaction. This unusual finding prompted us to perform further investigations in this area since 1,3,4-thiadiazines exhibit interesting biological properties. They have been reported to show cardiotonic, antihypertensive and spasmolytic activity and are the subject of many patents.[4] In some cases, antineoplastic effects have also been claimed.

Density functional calculations (DFT) show that two different mechanistic pathways are fundamentally possible for this ring transformation reaction (Scheme 2). The nucleophilic lone pair at the N-methyl nitrogen atom of **1** can attack isothiocyanate (**4**) to form a dipolar intermediate (**6**). The sulfur atom in this ambidentate species then attacks the ring carbon, thus expanding the ring to yield six-membered heterocycles of type (**5**). A valid alternative is a thermochemically allowed electrocyclic ring-opening of **1** to yield an intermediate ketene imine (**7**) which then reacts with **4** *via* a Diels-Alder reaction to yield **5**.



Scheme 2. Ring transformation mechanism according to B3LYP/6-31+G(dp) calculations

The DFT calculations indicate that the N-acylation pathway over **6** should be preferred at lower temperatures. The electrocyclic ring opening/cycloaddition pathway will require a slightly higher temperature. Although our calculations predict 1,2-diaza-1,3-dienes containing an alkylazo and a ketene imine substructure to be stable intermediates; they have not yet been experimentally observed. However, thermolysis experiments on the diazetine (**1**) in various solvents lead to product mixtures that, after separation, showed MS spectra that support the intermediate formation of **7**. Further support of this pathway is provided in that iminoketenes of type (**9**) (Scheme 3) have been postulated to be intermediates in the thermally allowed [π^2s + π^2a] – cycloreversion processes of azetin-2-ones[5] and their benzo-fused derivatives **8**.[6]

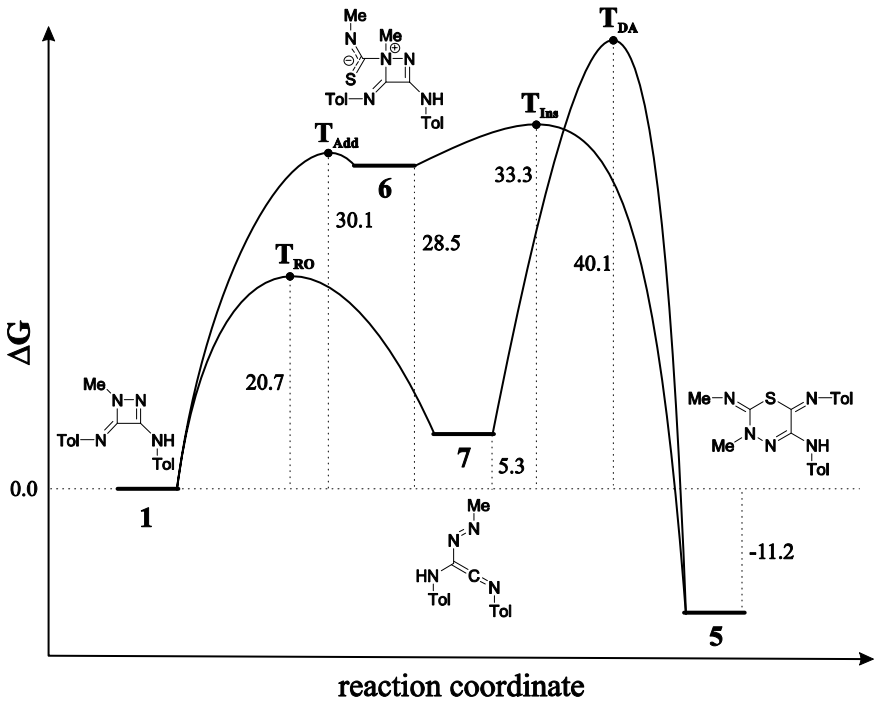
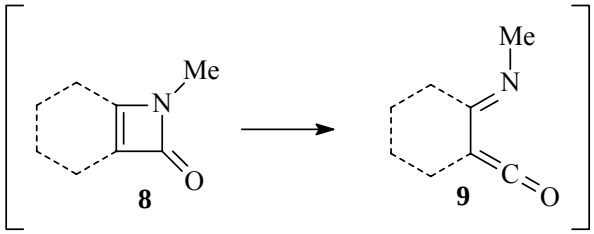


Figure 2. Reaction coordinate of ring transformation according to B3LYP/6-31+G(d,p) calculations. All Gibb's free energy values are given in kcal/mol.

We are currently performing an extensive spectroscopic and mechanistic investigation of this ring transformation reaction that will be reported in an upcoming article.



Scheme 3. Postulated iminoketene intermediate (**9**)

EXPERIMENTAL

General: All reagents were of commercial quality (Aldrich, Lancaster, Fluka, Merck). Reactions were carried out under argon atmosphere and monitored by TLC, on aluminium plates coated with silica (type 60 from Fluka). Column chromatography was carried out on silica (Fluka, silica 60, particle size 0.063- 0.2 mm). Melting points were measured with a B-545 (Boetius system) from Buechi, and are uncorrected. The ^{1}H- and ^{13}C NMR spectra were obtained with a Bruker AC 250 (250 MHz) spectrometer. MS spectra were taken from measurements with a Hewlett Packard LD/MSD 1100 mass spectrometer. Elemental analyses were carried out with an automatic analyser Varion EL III from Elementar Analysensysteme GmbH.

Crystal Structure Determination:

Data collection: The data for compound (**3b**) were collected at 200 K on a Siemens SMART 1000 CCD-diffractometer fitted with a molybdenum tube (K_α, λ = 0.71073 Å) and a graphite-monochromator. The intensity data for the compounds (**5d**) and (**5e**) were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects. [7,8]

Structure Solution and Refinement: The structures were solved by direct methods (SHELXS [9]) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97 [10]). For the amine group N5 of compounds (**5d**) and (**5e**) the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. The other hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.[10] XP (SIEMENS Analytical X-Ray Instruments, Inc.) was used for structure representations.

Crystal Data for **3b** [11]: $C_{24}H_{23}N_5O_3$, M = 429.5, orthorhombic, a = 5.689(5), b = 16.748(14), c = 22.262(17) Å, α = 90.00, β = 90.00, γ = 90.00, V = 2121.0(3) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.345 g cm^{-3}, F(000) = 904, Absorp. coeff. = 0.092 mm^{-1}, Crystal size = 0.5 × 0.05 × 0.05 mm^3, No. of reflections: collected:

14321, unique: 5146, observed: 2298 [$I > 2\sigma(I)$], R_1 [$I > 2\sigma$] = 0.0446, wR_2 = 0.0760 (all data against F^2). *Crystal Data for* **5d** [11] $C_{25}H_{25}N_5S$, Mr = 427.56 gmol^{-1}, light yellow prism, size 0.04 x 0.04 x 0.02 mm^3, triclinic, space group P-1, a = 9.9796(6), b = 10.0460(4), c = 12.9366(7) Å, α = 75.779(3), β = 69.237(2), γ = 66.622(3)°, V = 1104.81(10) Å^3 , T= -90 °C, Z = 2, ρ_{calcd} = 1.285 gcm^{-3}, μ (Mo-K_α) = 1.69 cm^{-1}, F(000) = 452, 7876 reflections in h(-12/12), k(-12/13), l(-16/15), measured in the range 2.23° ≤ Θ ≤ 27.50°, completeness Θ_{max} = 99 %, 5020 independent reflections, R_{int} = 0.030, 3595 reflections with $F_o > 4\sigma(F_o)$, 284 parameters, 0 restraints, $R1_{obs}$ = 0.053, wR^2_{obs} = 0.133, $R1_{all}$ = 0.083, wR^2_{all} = 0.150, GOOF = 1.040, largest difference peak and hole: 0.483 / -0.476 e Å^{-3}.
Crystal Data for **5e** [11]: $C_{22}H_{25}N_5O_2S$, Mr = 423.53 gmol^{-1}, light yellow prism, size 0.03 x 0.03 x 0.02 mm^3, triclinic, space group P-1, a = 7.4998(3), b = 12.0425(6), c = 12.1455(5) Å, α = 85.953(2), β = 87.992(2), γ = 84.578(3)°, V = 1088.86(8) Å^3 , T= -90 °C, Z = 2, ρ_{calcd} = 1.292 gcm^{-3}, μ (Mo-K_α) = 1.77 cm^{-1}, F(000) = 448, 7827 reflections in h(-9/9), k(-13/15), l(-15/15), measured in the range 1.70° ≤ Θ ≤ 27.46°, completeness Θ_{max} = 99.4 %, 4965 independent reflections, R_{int} = 0.025, 3713 reflections with $F_o > 4\sigma(F_o)$, 275 parameters, 0 restraints, $R1_{obs}$ = 0.052, wR^2_{obs} = 0.137, $R1_{all}$ = 0.077, wR^2_{all} = 0.154, GOOF = 1.016, largest difference peak and hole: 0.433 / -0.390 e Å^{-3}.

*General procedure for the synthesis of derivatives **(3)** and **(5)**:* A solution of 25 mL of THF and Δ^2-1,2-diazetine **(1)** (2 mmol) was cooled to -20°C and a solution of the corresponding isocyanate **(2)** or isothiocyanate **(4)** (2 mmol) in 5 mL of THF was added dropwise. After the addition, the reaction mixture was warmed up to rt and stirred for 6 h. Then the solvent was removed *in vacuo* and the residue was purified by recrystallization from heptane.

3,4-Bis(4-tolylimino)-2-methyl-N-(4-tolyl)-1,2-diazetidine-1-carboxamide **(3a)**: Yield 0.67g (81%), yellow crystals, mp 99°C. - ^{1}H-NMR (250 MHz, THF-d_8): δ = 9.18 (s, 1H, NH), 7.78-7.74 (m, 2H, CH), 7.49-7.46 (m, 2H, CH), 7.20-7.09 (m, 9H, CH), 2.90 (s, 3H, CH_3-N), 2.33 (s, 6H, CH_3), 2.28 (s, 3H, CH_3) ppm. - MS m/z: 412 [$M+H^+$], 90. - Anal. Calcd for $C_{25}H_{25}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 72.82; H, 5.89; N, 16.38.

(3Z,4E)-3,4-Bis(4-methoxyphenylimino)-2-methyl-N-phenyl-1,2-diazetidine-1-carboxamide **(3b)**: Yield 0.73g (85%), yellow crystals, mp 125°C (decomp). - ^{1}H-NMR (250 MHz, THF-d_8): δ = 9.25 (s, 1H, NH), 7.89-7.85 (m, 2H, CH), 7.56-7.52 (m, 2H, CH), 7.26-7.15 (m, 4H, CH), 6.99-6.85 (m, 5H, CH), 3.72 (s, 6H, CH_3-O), 2.88 (s, 3H, CH_3-N) ppm. - ^{13}C-NMR (63 MHz, THF-d_8,): δ = 160.1, 159.1, 152.2, 151.9, 146.1, 139.2, 137.4, 136.7, 129.5, 127.7, 125.2, 123.9, 119.6, 114.9, 114.4, 55.6, 55.5, 40.4 ppm. - MS m/z: 430 [$M+H^+$]. - Anal. Calcd for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.40; N, 16.31. Found: C, 67.23; H, 5.19; N, 16.08.

3,4-Bis(p-tolylimino)-2-methyl-N-phenyl-1,2-diazetidine-1-carboxamide **(3c)**: Yield 0.57g (72%), yellow needles, mp 113°C (decomp). - ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H, NH), 7.71-7.69 (m, 2H, CH), 7.56-7.54 (m, 2H, CH), 7.39-7.08 (m, 9H, CH), 2.97 (s, 3H, CH_3-N), 2.40 (s, 3H, CH_3), 2.37 (s, 3H, CH_3) ppm. - ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.6, 151.4, 146.1, 140.8, 139.8, 137.8, 137.5, 136.2, 129.6, 129.1, 128.4, 124.9, 124.0, 122.6, 119.5, 40.8, 21.4, 21.1 ppm. - MS m/z: 397 [M+H$^+$], 278, 235, 161, 146, 119, 91. - Anal. Calcd for $C_{24}H_{23}N_5O$: C, 72.52; H, 5.83; N, 17.62. Found: C, 72.38; H, 5.78; N, 17.37.

3,6-Dihydro-5-(4-methoxyphenylamino)-6-(4-methoxyphenylimino)-3-methyl-2-phenylimino-2H-1,3,4-thiadiazine **(5a)**: Yield 0.76 g (85%), orange powder, mp 134 °C. - ^{1}H-NMR (250 MHz, THF-d_8): δ = 7.99 (s, 1H, NH), 7.60-7.56 (m, 2H, CH), 7.20-7.14 (m, 2H, CH), 6.95-6.73 (m, 9H, CH), 3.75 (s, 3H, CH_3-O), 3.73 (s, 3H, CH_3-O), 3.63 (s, 3H, CH_3-N) ppm. - ^{13}C-NMR (63 MHz, THF-d_8): δ = 158.8, 155.7, 148.5, 144.4, 141.8, 136.4, 134.4, 129.7, 123.8, 122.3, 122.2, 120.9, 115.1, 114.4, 55.3, 43.1 ppm. – MS m/z: 446 [M+H$^+$], 90. - Anal. Calcd for $C_{24}H_{23}N_5O_2S$: C, 64.70; H, 5.20; N, 15.72; S 7.20. Found: C, 64.81; H, 4.97; N, 15.53; S, 7.25.

3,6-Dihydro-2-ethylimino-3-methyl-5-(4-tolylamino)-6-(4-tolylimino)-2H-1,3,4-thiadiazine **(5b)**: Yield 0.59 g (81%), orange powder, mp 147 °C. - ^{1}H-NMR (250 MHz, THF-d_8): δ = 7.88 (s, 1H, NH), 7.53-7.49 (m, 2H, CH), 7.23-7.20 (m, 2H, CH), 7.06-7.03 (m, 2H, CH), 6.87-6.84 (m, 2H, CH), 3.48 (s, 3H, CH_3-N), 3.09 (q, J = 7.1 Hz, 2H, CH_2-N), 2.34 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.14 (t, J = 7.1 Hz, 3H, CH_3) ppm. - ^{13}C-NMR (63 MHz, THF-d_8): δ = 146.1, 140.3, 138.9, 135.2, 134.2, 131.4, 130.5, 129.6, 120.2, 119.0, 44.2, 42.6, 20.9, 20.6, 16.6 ppm. - MS m/z: 366 [M+H$^+$], 90. - Anal. Calcd for $C_{20}H_{23}N_5S$: C, 65.72; H, 6.34; N, 19.16; S 8.77. Found: C, 65.60; H, 6.40; N, 19.33; S, 8.65.

2-Allylimino-3,6-dihydro-3-methyl-5-(4-tolylamino)-6-(4-tolylimino)-2H-1,3,4-thiadiazine **(5c)**: Yield 0.62 g (82%), orange crystals, mp 116 °C. - ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.66 (s, 1H, NH), 7.50-7.47 (m, 2H, CH), 7.27-7.24 (m, 2H, CH), 7.15-7.12 (m, 2H, CH), 6.90-6.87 (m, 2H, CH), 5.95 (m, 1H, CH), 5.17 (m, 2H, CH_2), 3.83 (m, 2H, CH_2-N), 3.63 (s, 3H, CH_3-N), 2.41 (s, 3H, CH_3), 2.34 (s, 3H, CH_3) ppm. - ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 144.9, 144.7, 141.7, 137.5, 135.7, 135.5, 133.2, 130.8, 130.0, 129.3, 119.7, 118.2, 114.9, 51.2, 42.9, 20.7, 20.6 ppm. – MS m/z: 378 [M+H$^+$], 90. - Anal. Calcd for $C_{21}H_{23}N_5S$: C, 66.81; H, 6.14; N, 18.55; S, 8.49. Found: C, 66.74; H, 6.09; N, 18.45; S, 8.60.

2-Benzylimino-3,6-dihydro-3-methyl-5-(4-tolylamino)-6-(4-tolylimino)-2H-1,3,4-thiadiazine **(5d)**: Yield 0.74 g (87%), yellow crystals, mp 138 °C. - ^{1}H-NMR (400 MHz, THF-d_8): δ = 7.92 (s, 1H, NH), 7.54-7.52 (m, 2H, CH), 7.32-7.30 (m, 2H, CH), 7.25-7.22 (m, 4H, CH), 7.16-7.12 (m, 1H, CH), 7.07-7.05 (m, 2H,

CH), 6.89-6.87 (m, 2H, CH), 4.31 (s, 2H, CH_2), 2.51 (s, 3H, CH_3-N), 2.35 (s, 3H, CH_3), 2.27 (s, 3H, CH_3) ppm. - ^{13}C-NMR (100 MHz, THF-d_8): δ = 146.2, 145.7, 141.7, 141.5, 139.0, 136.0, 134.6, 131.0, 130.7, 129.7, 128.7, 127.9, 126.9, 120.4, 119.2, 53.0, 42.9, 21.0, 20.9 ppm. - MS m/z: 427 [M+H$^+$], 336, 310, 277, 235, 161, 132, 118, 91. - Anal. Calcd for $C_{25}H_{25}N_5S$: C, 70.23; H, 5.90; N, 16.38; S 7.50. Found: C, 70.18; H, 6.08; N, 16.51; S, 7.36.

3,6-Dihydro-2-ethoxycarbonylmethylenimino-3-methyl-5-(4-tolylamino)-6-(4-tolylimino)-3H-1,3,4-thiadiazine **(5e)**: Yield 0.71 g (84%), yellow crystals, mp 123 °C. - ^{1}H-NMR (400 MHz, THF-d_8): δ = 7.92 (s, 1H, NH), 7.53-7.51 (m, 2H, CH), 7.23-7.21 (m, 2H, CH), 7.06-7.04 (m, 2H, CH), 6.87-6.85 (m, 2H, CH), 4.08-4.05 (q, 2H, J = 7.2 Hz, CH_2-OEt), 3.91 (s, 2H, CH_2), 2.5 (s, 3H, CH_3-N), 2.34 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.19 (t, 3H, J = 7.2 Hz, CH_3) ppm. - ^{13}C-NMR (100 MHz, THF-d_8): δ = 169.9, 146.1, 145.3, 143.7, 138.9, 136.1, 134.9, 131.1, 130.7, 129.7, 120.4, 119.3, 60.8, 51.3, 42.8, 20.9, 20.7, 14.4 ppm. - MS m/z: 423 [M+H$^+$], 350, 306, 277, 233, 161, 132, 118, 91. - Anal. Calcd for $C_{22}H_{25}N_5O_2S$: C, 62.38; H, 5.95; N, 16.54; S 7.57. Found: C, 62.45; H, 6.17; N, 16.70; S, 7.31.

3,6-Dihydro-3-methyl-2-methylimino-5-(4-tolylamino)-6-(4-tolylimino)-2H-1,3,4-thiadiazine **(5f)** :Yield 0.66 g (93%), orange crystals, mp 134 °C. - ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.55 (s, 1H, NH), 7.39-7.35 (m, 2H, CH), 7.17-7.14 (m, 2H, CH), 7.04-7.01 (m, 2H, CH), 6.80-6.77 (m, 2H, CH), 3.47 (s, 3H, CH_3-N), 2.90 (s, 3H, CH_3-N), 2.31 (s, 3H, CH_3), 2.23 (s, 3H, CH_3) ppm. - ^{13}C-NMR (63 MHz, $CDCl_3$): δ = 145.0, 144.8, 142.7, 137.6, 135.6, 133.2, 130.9, 130.1, 129.4, 119.7, 118.2, 42.8, 36.0, 21.0, 20.7 ppm. - MS m/z: 351 [M+H$^+$], 268, 234, 161, 132, 118, 107, 91. - Anal. Calcd for $C_{19}H_{21}N_5S$: C, 64.93; H, 6.02; N, 19.93; S 9.12. Found: C, 64.82; H, 6.12; N, 19.53; S, 8.75.

COMPUTATIONAL DETAILS

The calculations reported here were performed with the B3LYP density functional using the Gaussian03 [12] program package. The 6-31+G(d,p) basis set was employed. The B3LYP/6-31+G(d,p) level has been reported to yield a average accuracy of ±2.8 kcal/mol for thermodynamic stabilities and ±4.2 kcal/mol for reaction barriers of organic compounds.[13] Default convergence criteria were used for all calculations. No symmetry was employed in any of the calculations. The calculated structures were characterized as minima or transition structures by calculating their vibrational frequencies. All relative stabilities reported are gas phase Gibb's free energies that contain standard thermochemical and vibrational corrections. Structural coordinates of the intermediates/transition structures found on the hypersurface can be obtained from the authors (J. Weston) upon request.

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