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Synthesis of Heterocycles by Intramolecular Nucleophilic Substitution at an Electron-Deficient sp^2 Nitrogen Atom

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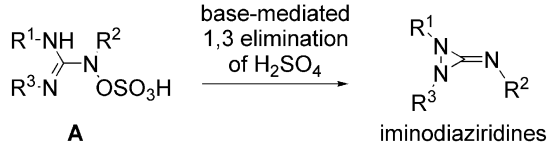
2-Aryl(arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones and 3-arylimino-6,7-dihydroimidazo[2,1-*c*]-[1,2,4]thiadiazoles have been synthesized by intramolecular nucleophilic substitution reactions at the electron-deficient sp^2 nitrogen atom of 2-(hydroxyimino)imidazolidine *O*-sulfonate. The displacement of the sulfate leaving group by both nitrogen and sulfur anionic nucleophiles proceeds exothermically by in-plane $S_N2\sigma$ nucleophilic substitution.

Introduction

Electrophilic amination is a long-established reaction in organic synthesis applied to the formation of C–N, N–N, O–N, S–N, S=N or P=N bonds.[1–9] In this process an electronegatively substituted nitrogen compound serves as the electrophilic [NH_2^+] equivalent (a^1 synthon) for the reaction with carbon, nitrogen, oxygen, sulfur or phosphorus nucleophiles.[10–17] Although there are many synthetic methods reported in the literature for the formation of [R_2N^+] synthons susceptible to nucleophilic attack, examples of intramolecular electrophilic amination reactions are rare. In this context, it is worth mentioning Sheradsky and Yusupova's synthesis of pyrrolidines[17a] and the recently described base-mediated 1,3-elimination of sulfuric acid from *N*-hydroxyguanidine *O*-sulfonic acids **A** (Scheme 1) leading to (alkylimino)diaziridines.[18]



Scheme 1. Reactivity of *N*-hydroxyguanidine *O*-sulfonic acids (**A**).

A conceptually interesting approach to electrophilic amination is based on nucleophilic substitution at the sp^2 N atom of ketone oximes **B**[19,20] or derivatives of 1,3-dioxolan-2-one oxime **C**[21] and imidazolidin-2-one oxime **D**[22] (Figure 1). The amination with oximes **A** was successfully applied to the formation of C–N bonds by an intermolecular S_N2-type reaction with organometallic reagents, the *O*-amination of alcohols and the preparation of a wide range of heterocycles (cyclic or spiro imines) by the Mizoroki–Heck, that is, amino-Heck, reaction. On the other hand, oxime derivatives **C** and **D** served as convenient substrates for the preparation of primary amines upon treatment with Grignard reagents and subsequent hydrolysis of the intermediary formed imines under acidic conditions.

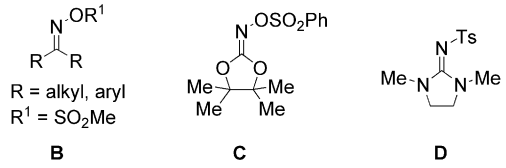


Figure 1. Compounds with electron-deficient sp^2-hybridized nitrogen atoms.

In contrast, there have only been a few reports on N–N, O–N and S–N bond formation at the electron-deficient oxime nitrogen.[19,22–24] Examples include the tandem nucleophilic addition–electrophilic amination reactions of cyclic hydroxyguanidine derivative **2** (Scheme 2) with aldehydes, carbon disulfide or Eschenmoser salts leading to novel bicyclic heterocycles with O–N, S–N or N–N bonds, respectively.[25,26] Note that an analogous reaction of **2** with phenyl isothiocyanate was not that straightforward. Indeed, it led to the initial formation of a nucleophilic addition product with a thioureido structure. However, this intermediate reacted with a second equivalent of isothiocyanate followed by cyclodesulfurization to give 3-phenyl-2-phenylimino-2,6,7,8-tetrahydroimidazo[1,2-*a*][1,3,5]triazine-4(3*H*)-thione.[25]

To the best of our knowledge, thus far no report has dealt with the electrophilic amination of ambident amido anions by compounds bearing an electron-deficient sp^2-

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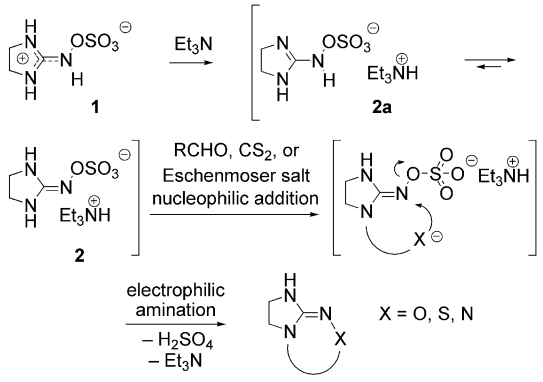
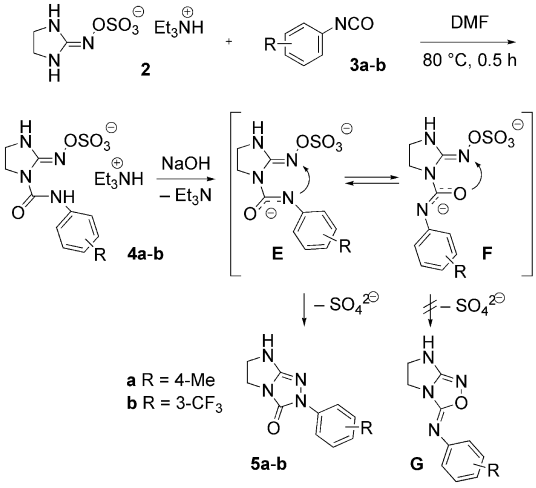


Scheme 2. Reactivity of triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate (**2**).



Scheme 3. Preparation of 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones (**5a**,**b**).

hybridized nitrogen atom. Therefore, in this paper, we wish to describe the domino nucleophilic addition–electrophilic amination reaction of 2-iminoimidazolidine **2** with aryl and arylsulfonyl isocyanates with a view to obtaining imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one derivatives that, by analogy to the well-known imidazo[2,1-*c*][1,2,4]triazoles and imidazo[2,1-*c*][1,2,4]triazin-4-ones,[27,28] may exhibit antibacterial and antiproliferative activities. Moreover, the newly prepared compounds, which are cyclic analogues of amidinoarylsulfonylureas, may behave as neuropeptide Y receptor (NPY) antagonists useful for the treatment of anxiety, obesity, hypertension and/or the regulation of coronary tone.[29] This synthetic strategy is based on the unique properties of **2**, which can be generated from betaine **1** by treatment with Et_3N and represents a cyclic guanidine derivative bearing a strong electron-withdrawing sulfate substituent at the exocyclic nitrogen atom N2. As described previously, the endocyclic nitrogen atoms N1 and N3 in **2** behave as nucleophiles, whereas the exocyclic N2 can react either with nucleophilic[25,26] or electrophilic[30,31] reagents.

Results and Discussion

As shown in Scheme 3, the reaction of triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate (**2**) with commercially available *p*-tolyl isocyanate (**3a**) in DMF at an elevated temperature led to the formation of the nucleophilic addition product **4a**, which was separated from the reaction mixture in its pure form in 75% yield. Then, upon treatment of an aqueous solution of the triethylaminium salt **4** with 10% NaOH at room temperature, an almost instantaneous reaction occurred to furnish 2-(4-methylphenyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (**5a**) in 90% yield as a result of facile N–N bond formation. From the above findings it may be inferred that the neutral ureide functionality is not susceptible to electrophilic amination by the sp^2-hybridized nitrogen and that a strong base was necessary to generate the ambident ureido anion **E**, which was immediately *N*-aminated with simultaneous extrusion of the SO_4^{2-} leaving group.

To improve the efficiency of the above chemical processes, a one-pot synthesis was performed in which the substrate **2** was subjected to successive reactions with aryl isocyanates and aqueous NaOH. In this manner compounds **5a** and **5b** were obtained in 71 and 68% yields, respectively (see the Exp. Sect.).

It should be emphasized that the amidate anion is ambident in nature and hence intramolecular electrophilic amination could occur at either the nitrogen or the oxygen atom of **E/F**. However, no *O*-amination product of type **G** (Scheme 3) was found in the reaction mixture. The structures of the *N*-amination products were confirmed by elemental analysis and IR and NMR spectroscopy of **5a**,**b** as well as by single-crystal X-ray analysis of compound **5a** (Figure 2).

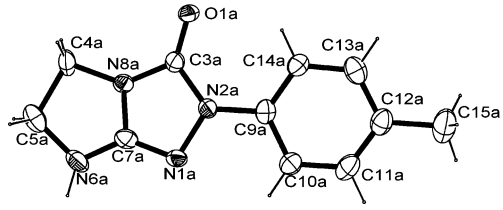
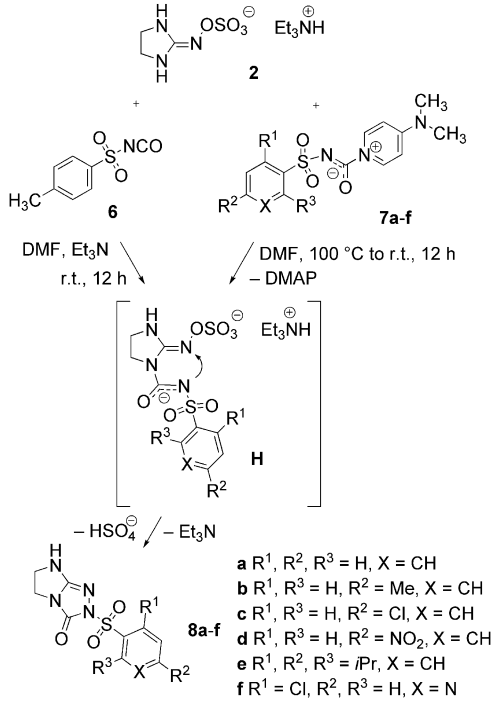


Figure 2. X-ray structure of **5a** (only the ordered molecule is shown).

The next logical step in the development of this chemistry was to study a similar reaction sequence by using arylsulfonyl isocyanates. As depicted in Scheme 4, for the above-mentioned purposes we used both the commercially available *p*-tolylsulfonyl isocyanate (**6**) and 4-(dimethylamino)pyridinium arylsulfonyl carbamoylides **7a**–**f**, easily-handled and indefinitely bench-top-stable under air substitutes of arylsulfonyl isocyanates prepared in our laboratories.[32,33] Thus, heating **2** with *p*-tolylsulfonyl isocyanate (**6**) in the presence of Et_3N and an analogous reaction with the arylsulfonyl carbamoylides furnished 2-(arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones **8a**–**f** in isolated yields of 23–69%. In this case the in-

termediary addition products **H** were not isolated from the reaction mixture. Apparently, the sulfonylureas **H**, which are stronger NH acids than the ureas **4** ($pK_a \approx 3$–4 vs. 13–14[34]), suffered deprotonation in the presence of triethylamine or DMAP to give ambident anions of type **H** which, by analogy to **4**, underwent regioselective *N*-amination to give the final bicyclic products **8**.



Scheme 4. Preparation of 2-arylsulfonyl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones (**8a**–**f**).

Again, the structures of compounds **8** bearing a N–N bond were confirmed by elemental analysis, IR and NMR spectroscopy as well as by X-ray diffraction analysis of **8c** (Figure 3). Note that the previously described approaches to the synthesis of similarly fused 1,2,4-triazole heterocyclic rings comprise the condensation reactions of 2-hydrazono-imidazolidines[27,28] or 2-hydrazono-hexahydropyrimidines.[35]

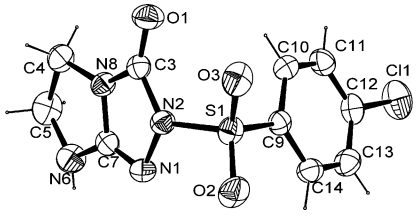
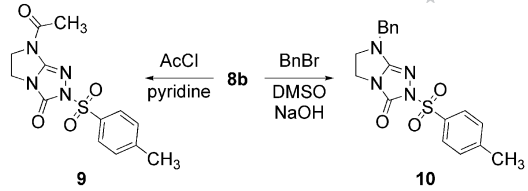


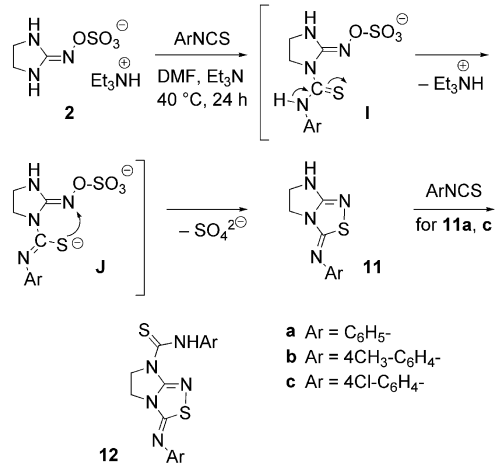
Figure 3. X-ray structure of **8c**.

To explore the reactivity of 2-(arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones of type **8** and to prove their chemical stability, we successfully prepared the acetyl and benzyl derivatives **9** and **10** (Scheme 5).



Scheme 5. Reactivity of 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (**8b**).

Having succeeded in the preparation of the desired imidazotriazolone derivatives **5** and **8**, we turned our attention to the less active aryl isothiocyanates. As stated in the Introduction, the previously described reaction of **2** with phenyl isothiocyanate carried out at room temperature consumed 3 mol-equiv. of isothiocyanate and afforded 3-phenyl-2-phenylimino-2,6,7,8-tetrahydroimidazo[1,2-*a*][1,3,5]triazine-4(3*H*)-thione.[25] We have now found that the same reaction performed in DMF at 40 °C for 12 h led to the formation of the desired *S*-amination product **12a** (Scheme 6). A similar result was observed by using 4-chlorophenyl isothiocyanate, which gave **12c**, the structure of which was confirmed unambiguously by single-crystal X-ray analysis (Figure 4). The less active 4-methylphenyl isothiocyanate gave 7-unsubstituted 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole (**11**). The use of 2 equiv. of isothiocyanates with **12a**,**c** prevented the formation of a mixture of **11** and **12**.



Scheme 6. Preparation of 6,7-dihydroimidazo[2,1-*c*][1,2,4]thiadiazoles **11b** and **12a**–**c**.

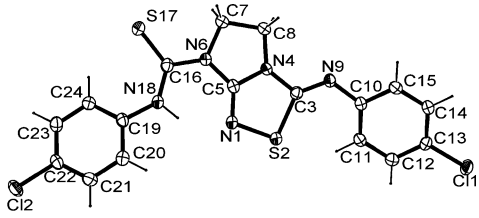


Figure 4. X-ray structure of **12c**.

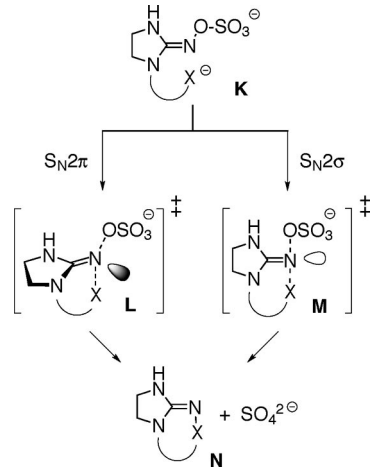
Computational Studies

It is generally accepted that the alkylation of neutral amides usually proceeds at the oxygen atom with *N*-substi-

tution arising from a subsequent rearrangement,[36] whereas the corresponding ambident anions, generated by the treatment of amides with strong bases, react with alkylating agents to give *N*-substituted products.[37,38] A similar reaction of amide anions with electrophilic carbenes leads to the formation of both *N*-substituted amides and *O*-substituted imidates.[39]

However, from a mechanistic point of view it should be noted that the electrophilic amination of anions of type **E**, **H** and **J** may be regarded as an intramolecular nucleophilic substitution at the sp^2-hybridized nitrogen atom. Several reports have been published on such processes including those of Narasaka and co-workers who found that substitution at the nitrogen atom of *O*-protonated oximes may occur easily in an S_N2 manner.[40] Moreover, based on the knowledge of heterocyclic chemistry, the well-known Boulton–Katritzky rearrangement can formally be written as an intramolecular nucleophilic substitution that proceeds according to a unimolecular one-step mechanism,[41–44] which, in turn, bears a resemblance to the recently investigated vinylic S_N2 reactions at carbon atoms.[45–51]

On the basis of this knowledge, substitution of the sulfate leaving group by the amidate anion at the sp^2-hybridized N2 nitrogen atom in **2** may proceed either by an $S_N2\pi$ mechanism (out-of-plane nucleophilic attack) by interacting with the π* orbital of the imino group or by an $S_N2\sigma$ mechanism (in-plane attack) in which the nucleophile interacts with the σ* orbital of the imino nitrogen of the N–O bond (Scheme 7). To gain a mechanistic insight into these processes, theoretical studies of the transition states were undertaken (see the Exp. Sect. for computational details).



Scheme 7. Intramolecular nucleophilic substitution (S_N2) reaction by two different mechanisms.

As shown in Figure 5 and Table 1, the cyclization reactions of dianions **E**, **H** and **J** to the bicyclic compounds **5**, **8** and **11**, respectively, gave only the planar in-plane $S_N2\sigma$ transition states **TSE**, **TSH** and **TSJ**, all of which have sufficiently low activation energies ($\Delta G^{\ddagger}$ = 11.09, 23.74 and 15.32 kcal/mol, respectively) to undergo substitution reactions under mild reaction conditions. The displacement of the sulfate anion occurs in a nearly linear manner (N–N2–O ranges from 169.8 to 170.7° and S–N2–O 163.9°). The $p(\pi)$ atomic orbitals perpendicular to the imidazoline ring of the exocyclic C=N2 bond are not involved in any bond-building or -breaking processes of σ bonds. The "looseness"

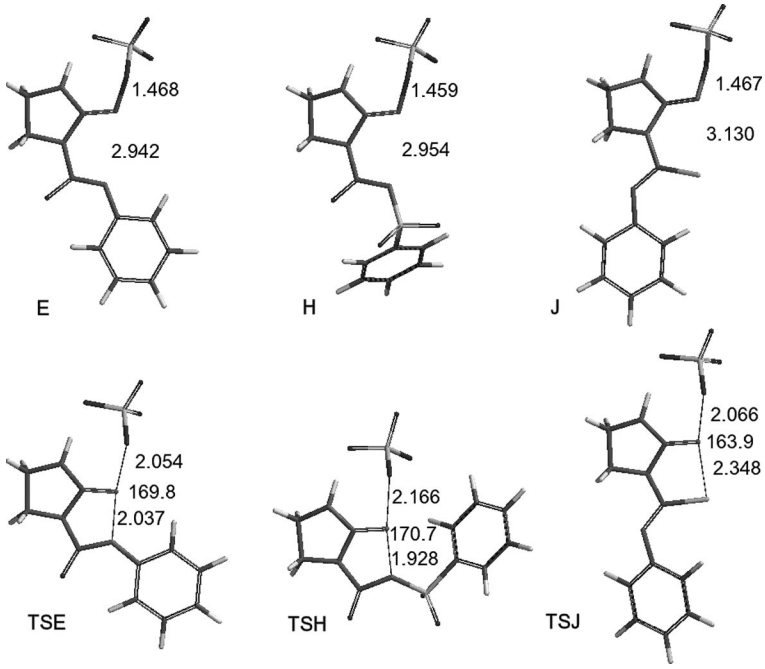


Figure 5. N–N, S–N and N–O atom distances and N–N–O and S–N–O bond angles calculated for the dianions **E**, **H** and **J** and the transition states **TSE**, **TSH** and **TSJ** by the B3LYP 6-31+G* method.

of these transition states correlates with the activation barriers, that is, the higher the barrier for the concerted S_N2 reaction, the larger the stretching of the N2–O bond in the transition-state structures.

Table 1. Electronic energy and Gibbs free-energy profiles (298.15 K) for the intramolecular S_N2 reactions calculated by the B3LYP 6-31+G* method using SM8[55] with H_2O (**5**) and DMF (**8**, **11a**) solvation models.[a]

Energy	**E**	**TSE**	**5**	**5** + SO_4^{2-}
E_e	–1380.70988	–1380.69326	–681.35760	–1380.79159
ΔE_e	0	10.43		–51.27
G^o	–1380.55066	–1380.53298	–681.19858	–1380.64552
ΔG	0	11.09		–59.52
Energy	**H**	**TSH**	**8**	**8** + SO_4^{2-}
E_e	–1929.28494	–1929.24747	–1229.94481	–1929.29895
ΔE_e	0	23.52		–8.79
G^o	–1929.11748	–1929.07965	–1229.78236	–1929.14879
ΔG	0	23.74		–19.64
Energy	**J**	**TSJ**	**11a**	**11a** + SO_4^{2-}
E_e	–1703.63582	–1703.61125	–1004.32236	–1703.67649
ΔE_e	0	15.42		–25.53
G^o	–1703.47746	–1703.45305	–1004.16961	–1703.53604
ΔG	0	15.32		–36.76

[a] Electronic energies and Gibbs free-energies are given in Hartrees. The relative energies (ΔE_e and ΔG) are given in kcal/mol.

All the investigated reactions are exothermic with ΔG ranging from –19.64 to –59.52 kcal/mol (Table 1). The reaction of the aryl amidate anion **E** has the lowest barrier and is considerably more exothermic than the corresponding reaction of the aryl thioamidate **J** and especially the arylsulfonyl amidate anion **H**.

Conclusions

The synthetically useful intramolecular nucleophilic substitution at an electron-deficient sp^2 nitrogen atom described herein represents a facile route to 2-aryl(arylsulfonyl)imidazo[2,1-*c*][1,2,4]triazol-3-ones **5** and **8** or 3-iminoimidazo[2,1-*c*][1,2,4]thiadiazoles **11**, which may find potential pharmaceutical use as antibacterial and antiproliferative agents or neuropeptide Y receptor (NPY) antagonists. Of the possible reaction mechanisms, the $S_N2\sigma$ pathway is feasible. This behaviour adds to the attractiveness of HN–C=N–O-containing azoles and may lead to a number of possible applications in heterocyclic synthesis.

Experimental Section

General: Melting points were determined with a Boëtius melting point apparatus. The IR spectra were recorded with a Thermo Scientific Nicolet FTIR spectrometer using a mixture of the compound and KBr. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or Varian Unity Plus 500 spectrometer. The chemical shifts were measured relative to the residual solvent signals at 2.50 or 7.26 ppm and 39.50 or 77 ppm, respectively. All reagents were used directly as obtained commercially. 2-Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**), triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate[25] (**2**) and the 4-(dimethylamino)pyridinium *N*-(arylsulfonyl)carbamoylides[32,33] **7** were prepared according to literature procedures.

Triethylaminium 1-(4-Methylphenylcarbamoyl)imidazolidin-2-ylideneaminosulfate (4a): 2-Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (1.4 mL, 10 mmol) were added to DMF (4 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. 4-Methylphenyl isocyanate (**3a**; 0.7 mL, 5.5 mmol) was introduced and the reaction mixture was kept at 80 °C for 0.5 h. Then the solution was cooled to 0 °C and the precipitated product **4a** was filtered and washed with acetone; yield 1.55 g (75%); m.p. 182–184 °C. ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 1.15 (t, J = 7.3 Hz, 9 H, CH_3), 2.25 (s, 3 H, CH_3), 3.07 (q, J = 7.3, 6 H, CH_2), 3.34 (t, J = 7.7 Hz, 2 H, CH_2), 3.82 (t, J = 7.7 Hz, 2 H, CH_2), 7.11 (d, J = 8.4 Hz, 2 H, CH), 7.19 (s, 1 H, NH), 7.34 (d, J = 8.4 Hz, 1 H, CH), 8.80 (br. s, 1 H, NH), 10.96 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 8.9, 20.7, 39.7, 44.0, 46.1, 118.7, 129.6, 131.8, 136.6, 150.1, 154.0 ppm. IR (KBr): $\tilde{\nu}$ = 3377, 3028, 2733, 1701, 1650, 1611, 1557, 1488, 1434, 1318, 1275, 1210, 1051 cm^{-1}. $C_{17}H_{29}ClN_5O_5S$ (415.51): calcd. C 49.14, H 7.03, N 16.85; found C 48.80, H 7.22, N 16.82.

General Procedure for the Synthesis of 2-Aryl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones (5): 2-Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (1.4 mL, 10 mmol) were added to DMF (4 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. The corresponding isocyanate (**3**; 0.7 mL, 5.5 mmol) was introduced and the reaction mixture was kept at 80 °C for 0.5 h. Then the reaction mixture was quenched with 5% NaOH (10 mL) and the precipitated product **5** was filtered and washed with water and acetone. Compound **5a** was also obtained in 90% yield by treatment of triethylaminium salt **4a** with 5% NaOH solution.

2-(4-Methylphenyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (5a): Yield 0.76 g (71%); m.p. 200–203 °C. ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 2.26 (s, 3 H, CH_3), 3.85 (s, 4 H, CH_2), 6.91 (s, 1 H, NH), 7.15 (d, J = 8.6 Hz, 1 H, CH), 7.65 (d, J = 8.6 Hz, 1 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.6, 40.2, 47.9, 117.0, 129.4, 132.3, 137.1, 148.9, 154.9 ppm. IR (KBr): $\tilde{\nu}$ = 3236, 2899, 1697, 1615, 1512, 1368, 1294, 819 cm^{-1}. $C_{11}H_{12}N_4O$ (216.24): calcd. C 61.10, H 5.59, N 25.91; found C 60.98, H 5.82, N 25.77.

2-[3-(Trifluoromethyl)phenyl]-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]-triazol-3(5*H*)-one (5b): Yield 0.92 g (68%); m.p. 159–165 °C. ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 3.89 (s, 4 H, CH_2), 7.11 (s, 1 H, NH), 7.41 (d, J = 7.8 Hz, 1 H, CH), 7.61 (t, J = 7.8 Hz, 1 H, CH), 8.06 (d, J = 7.8 Hz, 1 H, CH), 8.11 (s, 1 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 40.3, 47.9, 112.6 (q, J = 4 Hz), 119.4 (q, J = 4 Hz), 120.1, 130.4, 139.9, 149.1, 155.4 ppm. IR (KBr): $\tilde{\nu}$ = 3335, 2985, 2907, 1725, 1670, 1516, 1494, 1466, 1368, 1320, 1166, 1119 cm^{-1}. $C_{11}H_9F_3N_4O$ (270.21): calcd. C 48.89, H 3.36, N 20.73; found C 48.87, H 3.40, N 20.56.

General Procedure for the Synthesis of 2-(Arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones (8): 2-Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (1.4 mL, 10 mmol) were added to DMF (4 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. Subsequently, the corresponding car-

bamoylide **7** was added and the reaction mixture was heated at 100 °C with stirring for 5 min. When the carbamoylide had dissolved the heating and stirring were stopped and the solution was left at room temperature for 12 h. Then the solvent was evaporated under reduced pressure and the resulting residue was treated with methanol. The precipitated product **8** was washed with methanol followed by water and dried in vacuo. Compound **8b** was also obtained by using 4-methylbenzenesulfonyl isocyanate as a substrate.

2-(Phenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (8a): Yield 0.82 (62%); m.p. 246–252 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.73 (s, 4 H, CH$_2$), 7.22 (s, 1 H, NH), 7.60–7.88 (m, 5 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 39.7, 47.3, 127.3, 129.6, 134.4, 137.1, 148.8, 156.2 ppm. IR (KBr): $\tilde{\nu}$ = 3366, 2910, 1755, 1662, 1500, 1488, 1450, 1366, 1287, 1185, 1169, 1116, 1027, 880 cm^{-1}. $C_{10}H_{10}N_4O_3S$ (266.28): calcd. C 45.11, H 3.79, N 21.04; found C 44.93, H 3.97, N 20.86.

2-(4-Methylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (8b): Yield from ylide: 0.87 g (62%); yield from isocyanate: 0.93 g (66%); m.p. 262–268 °C. ^{1}H NMR (200 MHz, [D$_6$]-DMSO): δ = 2.35 (s, 3 H, CH$_3$), 3.82 (s, 4 H, CH$_2$), 7.23 (s, 1 H, NH), 7.42 (d, J = 8.4 Hz, 1 H, CH), 7.73 (d, J = 8.4 Hz, 1 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.1, 39.7, 47.3, 127.3, 130.0, 134.2, 145.1, 148.8, 156.1 ppm. IR (KBr): $\tilde{\nu}$ = 3377, 2913, 1748, 1669, 1498, 1459, 1365, 1289, 1188, 1171, 1116, 815 cm^{-1}. $C_{11}H_{12}N_4O_3S$ (280.30): calcd. C 47.13, H 4.32, N 19.99; found C 46.96, H 4.54, N 19.79.

2-(4-Chlorophenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (8c): Yield 1.04 g (69%); m.p. 264–269 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 3.74–3.76 (m, 4 H, CH$_2$), 7.28 (s, 1 H, NH), 7.74 (d, J = 8.3 Hz, 1 H, CH), 7.86 (d, J = 8.3 Hz, 1 H, CH) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 39.7, 47.3, 129.2, 129.8, 135.7, 139.4, 148.8, 156.4 ppm. IR (KBr): $\tilde{\nu}$ = 3365, 3091, 2911, 1741, 1622, 1503, 1475, 1380, 1288, 1187, 1012, 832, 757 cm^{-1}. $C_{10}H_9ClN_4O_3S$ (300.72): calcd. C 39.94, H 3.02, N 18.63; found C 39.71, H 3.30, N 18.48.

2-(4-Nitrophenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (8d): Yield 0.69 g (44%); m.p. 247–248 °C. ^{1}HNMR (200 MHz, [D$_6$]DMSO): δ = 3.75 (s, 4 H, CH$_2$), 7.34 (s, 1 H, NH), 8.12 (d, J = 7.8 Hz, 2 H, CH), 8.46 (d, J = 7.8 Hz, 2 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 40.1, 47.6, 125.2, 129.3, 142.2, 148.9, 151.0, 156.9 ppm. IR (KBr): $\tilde{\nu}$ = 3238, 2984, 2906, 1766, 1686, 1531, 1372, 1349, 1297, 1183, 1126, 740 cm^{-1}. $C_{10}H_9N_5O_5S$ (311.27): calcd. C 38.59, H 2.91, N 22.50; found C 38.14, H 3.20, N 22.19.

2-(2,4,6-Triisopropylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*]-[1,2,4]triazol-3(5*H*)-one (8e): Yield 0.45 g (23%); m.p. 180–182 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.15 (d, J = 6.8 Hz, 12 H, CH$_3$), 1.21 (d, J = 6.8 Hz, 6 H, CH$_3$), 2.93 (sept, J = 6.8 Hz, 1 H, CH), 3.79 (s, 4 H, CH$_2$), 4.22 (sept, J = 6.8 Hz, 2 H, CH), 7.19 (s, 1 H, NH), 7.29 (s, 2 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]-DMSO): δ = 23.6, 24.7, 28.9, 33.7, 40.1, 47.8, 124.2, 131.5, 148.2, 151.4, 154.2, 155.8 ppm. IR (KBr): $\tilde{\nu}$ = 3262, 3057, 2957, 2867, 1763, 1673, 1602, 1503, 1383, 1293, 1112 cm^{-1}. $C_{10}H_9N_5O_5S$ (392.52): calcd. C 58.14, H 7.19, N 14.27; found C 58.03, H 7.35, N 14.01.

2-(4-Chloropyridin-3-ylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*]-[1,2,4]triazol-3(5*H*)-one (8f): Yield 0.51 g (34%); m.p. 228 °C (dec.). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.82 (s, 4 H, CH$_2$), 7.31 (s, 1 H, NH), 7.88 (d, J = 5.4 Hz, 1 H, CH), 8.85 (d, J = 5.4 Hz, 1 H, CH), 9.01 (s, 1 H, CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 39.8, 47.4, 126.8, 131.6, 141.8, 147.8, 151.3, 155.7, 156.2 ppm. IR (KBr): $\tilde{\nu}$ = 3349, 3092, 1748, 1660, 1559, 1500, 1402, 1371, 1282, 1179 cm^{-1}. $C_9H_8ClN_5O_3S$ (301.71): calcd. C 35.83, H 2.67, N 23.21; found C 35.66, H 2.82, N 23.17.

7-Acetyl-2-(4-methylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*]-[1,2,4]triazol-3(5*H*)-one (9): 2-(4-Methylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (**8b**; 0.2 g, 0.714 mmol) was dissolved in pyridine (1 mL). The reaction mixture was cooled to 0 °C and acetyl chloride (0.25 mL, 3.5 mmol) was added dropwise with stirring. After 30 min the reaction mixture was quenched with water (1 mL) and evaporated under reduced pressure. The residue was dissolved in dichloromethane, filtered and purified on silica with the use of a chromatotron (ethyl acetate); yield 0.08 g (34.8%); m.p. 230–232 °C. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.44 (s, 3 H, CH$_3$), 2.48 (s, 3 H, CH$_3$), 3.88 (t, J = 7.4 Hz, 2 H, CH$_2$), 4.33 (t, J = 7.4 Hz, 2 H, CH$_2$), 7.36 (d, J = 8.4 Hz, 2 H, CH), 7.94 (d, J = 8.4 Hz, 2 H, CH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 22.2, 24.1, 38.6, 49.3, 128.6, 130.5, 134.8, 146.3, 148.3, 148.8, 168.1 ppm. IR (KBr): $\tilde{\nu}$ = 2929, 1756, 1706, 1651, 1504, 1457, 1372, 1303, 1178 cm^{-1}. $C_{13}H_{14}N_4O_4S$ (322.34): calcd. C 48.44, H 4.38, N 17.38; found C 48.41, H 4.33, N 17.26.

7-Benzyl-2-(4-methylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*]-[1,2,4]triazol-3(5*H*)-one (10): 2-(4-Methylphenylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (**8b**; 0.2 g, 0.714 mmol) was dissolved in DMSO (4 mL) and powdered NaOH (0.06 g, 1.5 mmol) was added with stirring. Subsequently benzyl bromide (0.128 mL, 1.07 mmol) was introduced dropwise. After 6 h of stirring the reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was dissolved in dichloromethane and purified on silica with the use of a chromatotron (ethyl acetate); yield 0.06 g (23.1%); m.p. 134–136 °C. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.46 (s, 3 H, CH$_3$), 3.63 (t, J = 7.3 Hz, 1 H, CH$_2$), 3.75 (t, J = 7.3 Hz, 1 H, CH$_2$), 4.37 (s, 2 H, CH$_2$), 7.24–7.26 (m, 2 H, CH), 7.33–7.35 (m, 3 H, CH), 7.36 (d, J = 8.3 Hz, 2 H, CH), 7.98 (d, J = 8.3 Hz, 2 H, CH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 22.2, 39.8, 49.6, 51.6. 128.6, 128.8, 128.9, 129.4, 130.2, 135.1, 135.3, 145.6, 149.5, 154.9 ppm. IR (KBr): $\tilde{\nu}$ = 3057, 2959, 1761, 1648, 1507, 1376, 1189, 1175 cm^{-1}. $C_{18}H_{18}N_4O_3S$ (370.43): calcd. C 58.36, H 4.90, N 15.12; found C 58.11, H 5.13, N 14.98.

***N*-(6,7-Dihydroimidazo[2,1-*c*][1,2,4]thiadiazol-3(5*H*)-ylidene)-4-methylaniline (11b):** 2-Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (0.8 mL, 5.7 mmol) were added to DMF (10 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. Subsequently, *p*-tolyl isothiocyanate (0.75 g, 5 mmol) was added and the reaction mixture was heated at 40 °C with stirring for 12 h. Then the solvent was evaporated under reduced pressure and the resulting residue was treated with methanol. The precipitated product **11b** was washed with 5% NaOH solution and water. The crude product was crystallized from DMF and dried in vacuo; yield 0.23 g (18%); m.p. 208–209 °C (DMF). ^{1}H NMR (200 MHz, [D$_6$]-DMSO): δ = 2.25 (s, 3 H, CH$_3$), 3.89 (s, 4 H, CH$_2$), 6.80 (d, J = 8.0 Hz, 2 H, CH$_2$), 7.10 (d, J = 8.0 Hz, 2 H, CH), 7.33 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.7, 41.6, 47.0, 120.8, 130.0, 132.26, 147.36, 157.5, 158.7 ppm. IR (KBr): $\tilde{\nu}$ = 3189, 1648, 1627, 1599, 1483 cm^{-1}. MS (EI): m/z = 232 (100) [M]$^+$. $C_{11}H_{12}N_4S$ (232.30): calcd. C 56.87, H 5.21, N 24.12; found C 56.58, H 5.30, N 23.95.

***N*-Phenyl-3-(phenylimino)-5,6-dihydro-7*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-7-carbothioamide (12a):** Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (0.8 mL, 5.7 mmol) were added to DMF (10 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. Subsequently phenyl isothiocyanate (1.2 mL, 10 mmol) was added and the reaction mixture was heated at 40 °C with stirring for 12 h. Then the solvent was evaporated under reduced pressure and the resulting residue was treated with methanol. The precipitated product **12a** was washed with a 5% NaOH solution and water. The crude product was crystallized from DMF and dried in vacuo; yield 0.9 g (51%); m.p. 188–189 °C (DMF). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.20 (t, J = 7.8 Hz, 2 H, CH_2), 4.88 (t, J = 7.8 Hz, 2 H, CH_2), 7.08 (d, J = 7.8 Hz, 2 H, CH), 7.20 (t, J = 7.3 Hz, 1 H, CH), 7.28–7.30 (m, 2 H, CH), 7.38–7.44 (m, 3 H, CH), 7.59 (d, J = 7.3 Hz, 2 H, CH), 11.17 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.3, 53.5, 121.0, 124.9, 125.0, 126.0, 129.2, 129.9, 138.3, 148.7, 150.9, 156.3, 176.3 ppm. IR (KBr): $\tilde{\nu}$ = 1616, 1583, 1570, 1480, 1433 cm^{-1}. MS (EI): m/z = 353 (100) $[M]^+$, 218 (99.5) $[M - PhNCS]^+$, 135 (25.8). $C_{17}H_{15}N_5S_2$ (353.46): calcd. C 57.77, H 4.28, N 19.81; found C 57.68, H 4.29, N 19.66.

***N*-(4-Chlorophenyl)-3-(4-chlorophenylimino)-7*H*-imidazo[2,1-*c*]-[1,2,4]thiadiazole-7-carbothioamide (12c):** Hydroxyamino-4,5-dihydroimidazolium *O*-sulfonate (**1**; 0.9 g, 5 mmol) and triethylamine (0.8 mL, 5.7 mmol) were added to DMF (10 mL). The suspension was stirred at room temperature for 3 min until a clear solution of the triethylaminium 2-(hydroxyimino)imidazolidine *O*-sulfonate salt (**2**) was formed. Subsequently, 4-chlorophenyl isothiocyanate (1.7 g, 10 mmol) was added and the reaction mixture was heated at 40 °C with stirring for 12 h. Then the solvent was evaporated under reduced pressure and the resulting residue was treated with methanol. The precipitated product **12c** was washed with a 5% NaOH solution and water. The crude product was crystallized from DMF and dried in vacuo; yield 0.41 g (19%); m.p. 208–209 °C (DMF). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.98–4.06 (m, 2 H, CH_2), 4.64–4.72 (m, 2 H, CH_2), 6.98–7.04 (m, 2 H, CH), 7.41–7.52 (m, 4 H, CH), 7.59–7.65 (m, 2 H, CH), 11.12 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 40.1, 54.2, 122.6, 126.6, 128.1, 128.9, 129.9, 130.5, 137.4, 147.9, 151.6, 165.5, 176,0. IR (KBr): $\tilde{\nu}$ = 1616, 1583, 1570, 1480, 1433 cm^{-1}. $C_{17}H_{13}Cl_2N_5S_2$ (422.35): calcd. C 48.34, H 3.10, N 16.58; found C 48.02, H 3.32, N 16.37.

Crystal Structure Determination: The diffraction data were collected with a KumaCCD diffractometer using graphite-monochromated Mo-K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis software.[52] The crystal structures were solved by direct methods with the SHELXS-97[53] program and refined by full-matrix least-squares methods on F^2 with SHELXL-97.[53]

Crystal Data for $C_{11}H_{12}N_4O$ (5a): Monoclinic, space group $P2_1$, a = 7.7698(4), b = 10.8378(6), c = 13.0522(7) Å, β = 104.260(5)°, V = 1065.23(10) Å^3, Z = 4, d_x = 1.348 g/cm, T = 130 K. Data were collected by using a crystal with dimensions 0.4 × 0.4 × 0.3 mm. The final R indices for 1730 reflections with $I>2\sigma(I)$ and 295 refined parameters are R_1 = 0.0483 and wR_2 = 0.1017 (R_1 = 0.0551 and wR_2 = 0.1039 for all 1975 data). The structure was initially refined in the $P2_1/c$ space group (with all molecules disordered). Refinement in the $P2_1$ symmetry showed that symmetry of the inversion centre is broken because only one half of the molecules in the crystal are disordered.[54]

Crystal Data for $C_{10}H_9ClN_4O_3S$ (8c): Triclinic, space group $P\bar{1}$, a = 7.3682(3), b = 8.3024(5), c = 9.9066(3) Å, α = 94.396(4), β = 100.569(4), γ = 92.532(4)°, V = 592.94(5) Å^3, Z = 2, d_x = 1.684 g/cm^3, T = 294 K. Data were collected by using a crystal with dimensions 0.5 × 0.15 × 0.10 mm. Final R indices for 1890 reflections with $I>2\sigma(I)$ and 172 refined parameters are R_1 = 0.0299 and wR_2 = 0.0809 (R_1 = 0.0416 and wR_2 = 0.0867 for all 2412 data).[54]

Crystal Data for $C_{17}H_{13}Cl_2N_5S_2$ (12c): Monoclinic, space group $P2_1/c$, a = 10.5880(6), b = 14.5965(7), c = 11.5524(6) Å, β = 101.268(5)°, V = 1750.98(16) Å^3, Z = 4, d_x = 1.602 g/cm^3, T = 193 K. Data were collected by using a crystal with dimensions 0.4 × 0.3 × 0.05 mm. The final R indices for 2956 reflections with $I>2\sigma(I)$ and 249 refined parameters are R_1 = 0.0325 and wR_2 = 0.0877 (R_1 = 0.0410 and wR_2 = 0.0920 for all 3554 data).[54]

Computational Methods: All the calculations presented in this paper were carried out with the Spartan 08 program package provided by Wavefunction, Inc.[56] The geometries were fully optimized in vacuo by using the DFT B3LYP method with the diffuse functions 6-31+G* basis set. Frequency calculations were performed for all structures to prove the energy minima. The geometries of the transition states found showed single imaginary frequencies pertaining to N–N or N–S bond formation and N–O bond breakage. The $S_N2\sigma$ reaction energy profiles were derived from calculations at the DFT B3LYP/6-31+G* level of theory with application of the water (formation of **5**) and DMF (formation of **8** and **11a**) SM8[55] solvation models. The Gibbs free energies were obtained from electronic energies corrected with zero-point vibrational energies (ZPE), thermal energies involving a temperature increase from 0 to 298.15 K and entropies. The relative energies were obtained by subtracting the energy of the lowest-energy structures (dianions) from the energies of all the other geometries and converting these differences into kcal/mol.

Supporting Information (see also the footnote on the first page of this article): B3LYP 6-31+G* geometries and imaginary frequencies for **TSE**, **TSH** and **TSJ** transition-state stationary points.

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