Tetrahedron 67 (2011) 3612–3618

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of aza-aromatic hydroxylamine-*O*-sulfonates and their application to tandem nucleophilic addition–electrophilic 5-*endo-trig* cyclization

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ARTICLE INFO

Article history:
Received 19 January 2011
Received in revised form 9 March 2011
Accepted 28 March 2011
Available online 2 April 2011

Keywords:
Hydroxylamine-*O*-sulfonic acid
HOSA
5-*endo-trig* Cyclization
Nucleophilic addition
Aza-aromatic hydroxylamine-*O*-sulfonic acids
Cytostatic activity

ABSTRACT

Hydroxylamine-*O*-sulfonic acid (HOSA) was used as an efficient nucleophilic amination reagent for 2-chloropyrimidines, 2-chloroquinolines, and 1-chloroisoquinoline. The newly obtained heteroaromatic hydroxylamine-*O*-sulfonates subjected to the reaction with acyl isothiocyanates underwent tandem nucleophilic addition–electrophilic 5-*endo-trig* cyclization. The mechanism of the cyclization was investigated with use of the long-range corrected hybrid density functional ωB97X-D/6-31+G* and SM8 (DMF) solvation model. The structures of the heteroaromatic hydroxylamine-*O*-sulfonates and *N*-(5-methoxy-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)benzamide were confirmed by single crystal X-ray analysis. *N*-(2*H*-[1,2,4]thiadiazolo[3,2-*a*]isoquinolin-2-ylidene)benzamide exhibited a pronounced in vitro cytostatic activity against human tumor cell lines SISO, LCLC, A-427, DAN-G, and RT-4 (IC_{50} in the range 1.47–2.97 μM).

1. Introduction

The development of novel transformations that allow the rapid construction of carbocyclic and heterocyclic scaffolds via 5-*endo-trig* cyclization from simple readily available starting materials is an active area of investigation.[1–3] Of special interest are electrophile-induced processes that do not violate the Baldwin's rules.[4] One of the most effective ways to achieve this goal can be to implement a reaction cascade involving mechanistically different processes in one pot. As a part of our ongoing program on hydroxylamine-*O*-sulfonates,[5,6] we have now designed a facile synthesis of 1,2,4-thiadiazole-fused ring systems via a tandem process consisting of nucleophilic addition and electrophilic 5-*endo-trig* cyclization using the previously unknown aza-aromatic hydroxylamine-*O*-sulfonates. We started our research by finding a suitable method for preparation of heteroaromatic amines with a good leaving group at the external nitrogen atom. It is astonishing that despite enormous progress made in the synthesis of heteroaryl amines,[7] no attention has been paid to aza-aromatic compounds bearing hydroxylamine-*O*-sulfonate functionality amenable to further transformations based on their dual electrophilic and nucleophilic properties. Therefore, we turned our attention to hydroxylamine-*O*-sulfonic acid (HOSA), a versatile commercially available inorganic aminating reagent with amino group behaving either as an electrophile or nucleophile.[8–10] The electrophilic properties of this reagent are observed under basic conditions, while the nucleophilic character is evident under neutral or acidic conditions.

2. Results and discussion

We reported on in an earlier paper that the nucleophilic amination of non-aromatic 2-chloro-4,5-dihydroimidazole with HOSA provides a suitable entry into otherwise inaccessible 2-(4,5-dihydroimidazolium)-hydroxylamine-*O*-sulfonate.[11] The present paper expands upon this investigation by showing that by a comparably mild synthesis starting from aza-aromatic chlorides **1**–**5**, a new class of 2-azinium-hydroxylamine-*O*-sulfonates **6**–**10** can be obtained in 59–77% yield by the treatment with two-fold excess of HOSA in aqueous or DMF solution at room temperature. The isolation of the products is very simple because they proved to be stable crystalline compounds that precipitate from the reaction mixture and can be easily purified by crystallization (Scheme 1).

We found that this nucleophilic substitution reaction is very sensitive to the acidity of the medium, since it was abolished upon addition of equimolar amount of triethylamine. Apparently, under the conditions of acid-catalyzed reaction, the electrostatic effect or

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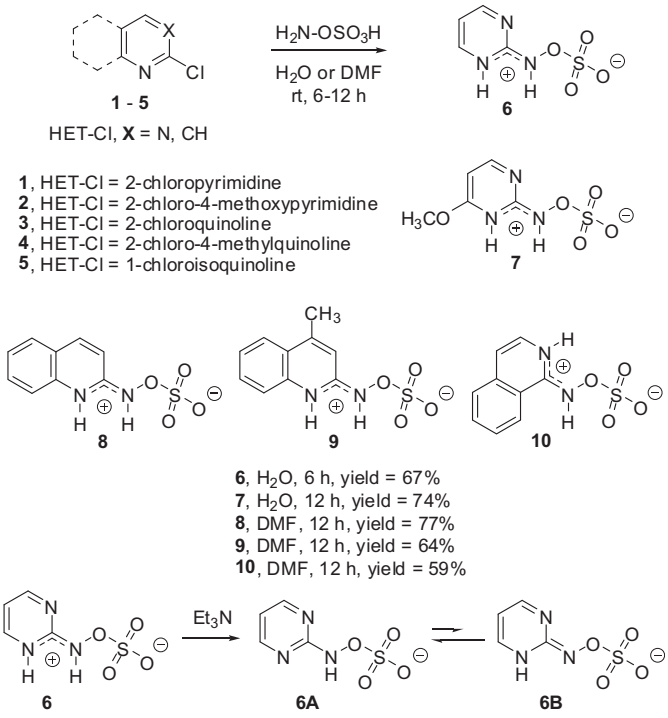
doi:10.1016/j.tet.2011.03.091



Scheme 1. Preparation of aza-aromatic hydroxylamine-*O*-sulfonates **6**–**10** via acid-catalyzed nucleophilic substitution.

hydrogen bonding of HOSA to the basic azine nitrogen facilitates chlorine substitution at the 2 position.

The structures of compounds **6**–**10** were fully characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy as well as by single crystal X-ray diffraction analysis of **6** and **7**. As seen in Fig. 1, in the solid state these compounds exist in zwitterionic form.

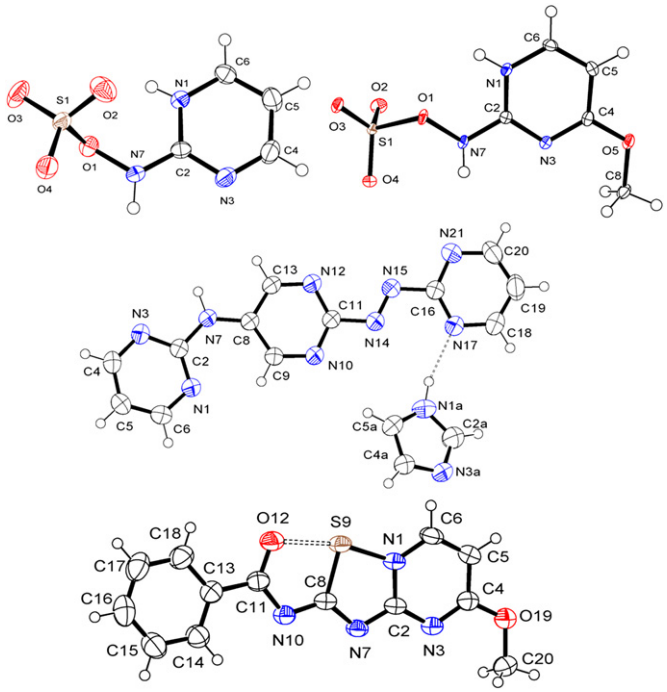
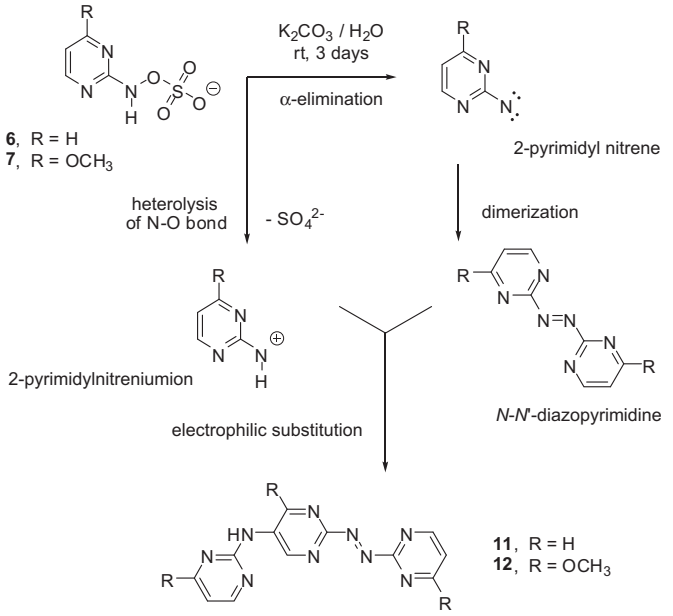


Fig. 1. Molecular structure of **6** (top left), **7** (top right), **11a** (middle), and **16** (bottom) with atom labeling scheme and displacement ellipsoids shown at the 50% probability level. The intramolecular O12···S9 contact is 2.1242(11) Å.

Betaine **6** upon treatment with triethylamine was further converted into the corresponding aminium salt, which can exist as either amino (**6A**) or imino (**6B**) tautomer. Optimization of the molecular structures of these species using DFT (B3LYP/6-31+G*) computations revealed that amino tautomer **6A** should prevail both in the gas phase and in DMF solution (Scheme 1).

Next, we have obtained experimental evidence of the ability of the newly prepared aza-aromatic hydroxylamine-*O*-sulfonates to serve as the precursors of heteroarylnitrenium ions by N–O bond heterolysis. As shown in Scheme 2, betaine **6** treated with aqueous K_2CO_3 solution at room temperature afforded compound **11** as a result of both heteroarylation of exocyclic divalent 2-pyrimidinylnitrenium ion and the coupling of nitrene species generated by α-elimination of hydrogen sulfate (Scheme 2). The structure of **11** was confirmed by IR and NMR spectroscopic data as well as by single crystal X-ray analysis of the complex **11a** obtained by co-crystallization with imidazole (Fig. 1).

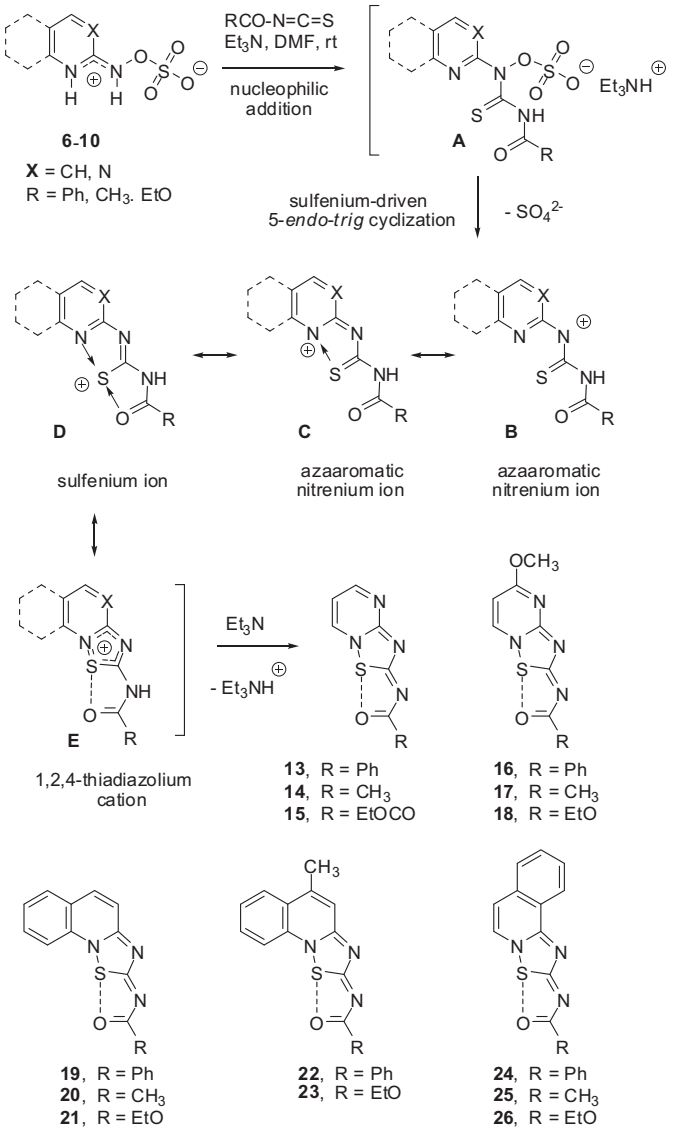


Scheme 2. Formation of (4-pyrimidylamino)-diazopyrimidines **11** and **12**.

In this context it is pertinent to note, that previously Takeuchi and Watanabe achieved N-arylation of 2-pyrimidylnitrenium ion generated from tetrazolo[1,5-*a*]pyrimidine in the presence of trifluoroacetic acid[12] and computational studies of heteroarylnitrenium ions were performed by Cramer, Favley, and Di Stefano.[13–16]

With aza-aromatic nitrenium ion precursors in hands, we have subjected compounds **6**–**10** to the reaction with a series of acyl isothiocyanates. As shown in Scheme 3, upon treatment of the triethylaminium sulfonates with corresponding heterocumulene in DMF solution at room temperature, a tandem nucleophilic addition–electrophilic 5-*endo*-*trig* cyclization took place resulting in the formation of 1,2,4-thiadiazolium cations **E**, which were further converted into fused [1,2,4]thiadiazole derivatives **13**–**26** by the treatment with triethylamine. Structure of these compounds was confirmed by IR, NMR spectroscopic data, and X-ray analysis of pyrimidine derivative **16** (Fig. 1).

Interestingly, the ωB97X-D/6-31+G* computational studies of the mesomeric species **B**–**E** revealed that all of them possess the positive charge of +0.697 e (natural) or +0.921 e (Mulliken) located on the sulfur atom, which indicates that contribution of resonance structure represented by the sulfenium ion **D** is significant. The calculated S–N distance of 1.78 Å is close to a single covalent bond



Scheme. 3. Formation of 1,2,4-thiadiazoles **13**–**26** via tandem nucleophilic addition–electrophilic 5-*endo-trig* cyclization.

(1.74 Å) and the distance of 2.358 Å between central sulfur atom and the oxygen atom of the neighboring C=O group is considerably shorter than the sum of van der Waals radii of a sulfur and an oxygen atom (3.25 Å). From the above results one could infer that self-destruction of the nitrenium ion **B** initially formed upon N–O bond heterolysis may lead to a highly electrophilic sulfenium ion **D**, which is stabilized by the neighboring sp^2-hybridized nitrogen and oxygen atoms of azine and carbonyl group, respectively. It is therefore pertinent to note that the electronic and molecular structure of the mesomer **D** bears resemblance to the previously described sulfenium,[17] tellurium,[18] and siliconium[19] ions stabilized by two neighboring dimethylaminoethyl groups. A characteristic feature of such structures is the strong dependence of stabilizing sulfur–nitrogen and sulfur–oxygen bond strengths and lengths on the valence state and electronegativity of the attached substituents. In the case of **B**–**E**, the S–N bond approaches values characteristic of covalent bond, while S–O interaction is typical of S–O hypervalent bond governed by the σ interaction between the nonbonding orbital of the oxygen atom and the *p* and *d* orbitals of sulfur atom.[20] Thus, the electronic and molecular structure of these species is best represented by the 1,2,4-thiadiazolium cation **E.**

As shown in Scheme 3, the central tent of the above reaction sequence is the initial nucleophilic addition of the exocyclic NH group to the C=N bond of heterocumulene with formation of the intermediate **A**, which, in turn, may suffer spontaneous heterolysis of the rather weak N–O bond. Since the reaction takes place in DMF solution (with its high dielectric constant), the formation of the SO_4^{2-} ion would not be highly endoenergetic.[21] Then, the electrophilic 5-*endo-trig* cyclization gives rise to the formation of highly acidic but stabilized 1,2,4-thiadiazolium cation of type **E**, which is expected to persist in polar solvent. Upon treatment of the reaction mixture with a second molar equivalent of triethylamine, the deprotonated free bases **13**–**26** are formed. According to calculations performed with long-range and dispersion-corrected ωB97X-D functional[22] with 6-31+G* basis set using SM8 (DMF) solvation model,[23] both the heterolysis of N–O bond and the proton abstraction are exothermic and the heats of these processes in DMF were estimated as 15.2 and 35.9 kcal/mol, respectively (Fig. 2).

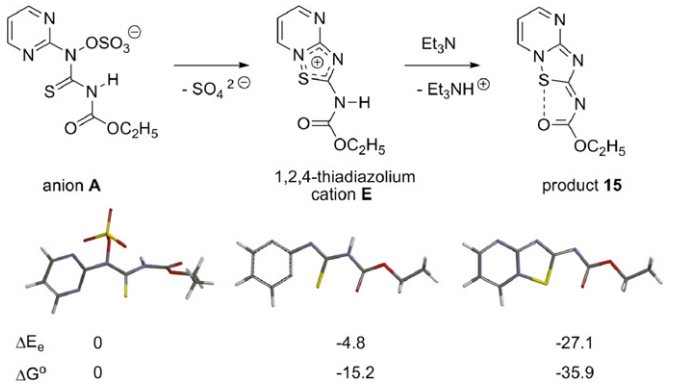


Fig. 2. The relative electronic energy (ΔE) and Gibbs free energy (ΔG) profiles (298.15 K, kcal/mol) for sulfenium-driven 5-*endo-trig* cyclization calculated with long-range and dispersion-corrected ωB97X-D functional[22] with 6-31+G* basis set using SM8[23] (DMF) solvation model.

To ensure that no alternative nucleophilic 5-*endo-trig* cyclization was taking place, we have carried out DFT calculations on the reaction pathway depicted in Fig. 3. A species of type **A** could suffer a base-promoted abstraction of the proton from the thiourea moiety to give the dianion **F**, which bears a nucleophilic sulfur at the homoallylic position suitable for 5-*endo-trig* cyclization via intramolecular concerted S_N2' reaction with loss of a SO_4^{2-} ion. Although we succeeded in finding the transition state **G** for this

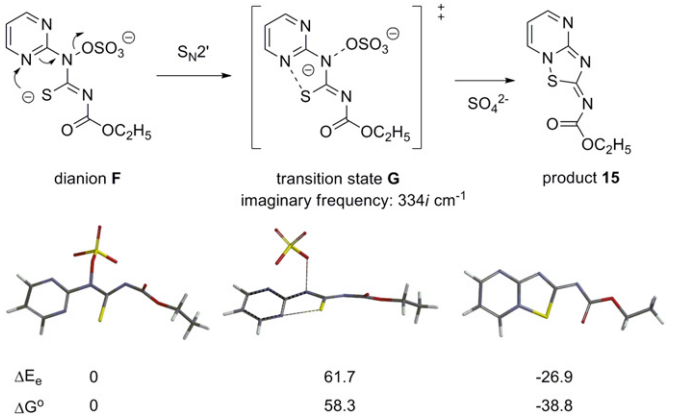


Fig. 3. The relative electronic energy (ΔE) and Gibbs free energy (ΔG) profiles (298.15 K, kcal/mol) for S_N2'-type 5-*endo-trig* cyclization calculated with long-range and dispersion-corrected ωB97X-D functional[22] with 6-31+G* basis set using SM8[23] (DMF) solvation model.

unusual process, it is prohibited by high energy barrier of 58.3 kcal/mol, and therefore, should not contribute to the observed mild cyclization (Fig. 3).

3. Conclusion

In conclusion, we have discovered a new reaction of hydroxylamine-*O*-sulfonic acid (HOSA) with aza-aromatic chlorides leading to the previously not described aza-aromatic hydroxylamine-*O*-sulfonates **6**–**10**, which may serve as useful precursors of aza-aromatic nitrenium and/or sulfenium ions. The tandem nucleophilic addition–electrophilic 5-*endo*-*trig* cyclizations of **6**–**10** have been explored and the mechanism has been proposed on the basis of DFT calculations. Given the fact that the field of aza-aromatic nitrenium ions is still in its infancy, we believe that the results described in this paper will stimulate further research on the development of new reactions. Additional studies are ongoing.

It is pertinent to note that 2-acylimino-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine derivatives are of considerable interest in medicinal chemistry, for instance as antimalarial agents and in the treatment of flu infections. Compounds **13** and **15** were prepared earlier by oxidation of N^1-(2-pyrimidyl)-N^2-benzoyl-thioureas with bromine.[24–26]

The compounds **21**, **24**, and **26** were evaluated for their cytotoxic activity against five human cancer cell lines: uterine cervical adenocarcinoma SISO, lung cancer LCLC and A-427, pancreas adenocarcinoma DAN-G, and neural cell line RT-4. They were examined for their potency of action at five successive concentrations in the range 1–20 μM. The average IC_{50} values obtained in these experiments are reported in Table 1. According to these results compounds **21** and **26** exhibit moderate activity (IC_{50} values in the range 2.93–23.14 μM), with the RT-4 cell line being the most affected. Compound **24** was the most potent but on the other hand the least selective one as it shows an antiproliferative activity against SISO cell line, which is weakly influenced by the remaining compounds. It appears that benzamide group in position 2 (compound **24**) is preferred over ethyl carbamate moiety (compounds **21** and **24**), which may suggest that lipophlicity of tested compounds plays important role.

Table 1
IC_{50} values (μM) ± S.D. in five human cancer cell lines being an average of **3**–**6** independent experiments

Compound	Cell lines				
	SISO	LCLC	A-427	DAN-G	RT-4
21	13.00±1.12	6.72±0.91	3.68±1.17	6.13±2.53	2.93±1.79
24	1.90±0.08	1.86±0.09	2.97±0.55	1.99±0.08	1.41±0.51
26	23.15±2.79	12.94±0.42	16.12±5.75	18.01±1.01	9.13±2.14

4. Experimental section

4.1. General

All the calculations presented in this paper were carried out with the Spartan 08 program package provided by Wavefunction, Inc. The geometries were fully optimized in vacuum with DFT ωB97X-D[22] or B3LYP method using diffuse functions 6-31+G* basis set. Frequency calculations were performed for all structures to prove the energy minima. The geometry of the transition state found showed single imaginary frequency pertaining the N–S bond formation and N–O bond breakage. The reaction energy profiles were derived from DFT ωB97X-D/6-31+G* calculations with application of DMF SM8[23] solvation models. The Gibbs free energies were obtained from the electronic energies corrected with the zero-point vibrational energies (ZPE), thermal energies involving temperature increase from 0 to 298.15 K and entropies. Relative energies were obtained by subtracting the energy of the lowest-energy structures (anion or dianion) from the energies of all the other geometries and converting these differences into kcal/mol.

4.2. Cytotoxic activity

All cell lines were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ) (Braunschweig, Germany). Cytotoxicity studies were performed with a well established microtiter assay based on the staining of adherent cells with crystal violet; the method has been described in detail in previous publications.[27] DMF stock solutions of the compounds were diluted 1000-fold in cell culture medium (RPMI 1640 medium supplemented with 10% FCS) to give the final test concentration. Cells were continuously exposed to compounds for 96 h at 37 °C in a humid atmosphere of 5% CO_2/air. The IC_{50} values were estimated by least squares analysis of the dose response curves to give the concentration of substance that inhibits cell growth by 50% compared to untreated controls. Reported IC_{50} values are the averages of 3–6 independent determinations.

4.3. General procedure for the heteroaromatic hydroxylamine-*O*-sulfonates 6–10

The corresponding chloroheteroaryl substrate (10 mmol) was stirred for 12 h at room temperature with hydroxylamine-*O*-sulfonic acid (2.26 g, 20 mmol) in water (2-chloropyrimidines, 5 mL) or DMF (2-chloroquinolines and 1-chloroisoquinoline, 5 mL). The precipitated product **6**–**10** was filtered and washed with a small portion of pure solvent. In the case of pyrimidin-1-ium-2-ylamino sulfate (**6**) the reaction mixture was filtered after 6 h. The products were dried in desiccator over P_2O_5 under vacuum and used without any further purification.

*4.3.1. Pyrimidin-1-ium-2-ylamino sulfate (**6**).* A white solid (1.28 g, 67%), mp 225 °C dec; [Found: C, 25.02; H, 2.72; N, 21.79. $C_4H_5N_3O_4S$ requires C, 25.13; H, 2.64; N, 21.98]; ν_{max} (KBr) 3200, 3110, 3033, 2895, 2827, 1625, 1543, 1453, 1337, 1291, 1250, 1207, 1047, 797, 709 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.07 (1H, t, *J* 5.2 Hz, C*H*), 8.64 (2H, d, *J* 5.2 Hz, C*H*), 12.40 (2H, br s, N*H*); δ_C (50 MHz, DMSO-d_6) 111.5, 155.4, 156.9.

*4.3.2. 4-Methoxypyrimidin-1-ium-2-ylamino sulfate (**7**).* A white solid (1.64 g, 74%), mp 212–216 °C; [Found C, 26.99; H, 3.31; N, 18.72. $C_5H_7N_3O_5S$ requires C, 27.15; H, 3.19; N, 19.00]; ν_{max} (KBr) 3114, 3028, 2958, 1637, 1490, 1398, 1287, 1264, 1201, 1186, 1060, 1004, 851, 825, 733, 629 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 3.97 (3H, s, OCH_3), 6.51 (1H, d, *J* 7.0 Hz, C*H*), 8.08 (1H, d, *J* 7.0 Hz, C*H*), 12.85 (2H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 56.3, 101.3, 146.7, 156.0, 172.1.

*4.3.3. Quinolinium-2-ylamino sulfate (**8**).* A white solid (1.85 g, 77%), mp 210 °C dec; [Found C, 45.12; H, 3.41; N, 11.62. $C_9H_8N_2O_4S$ requires C, 45.00; H, 3.36; N, 11.66]; ν_{max} (KBr) 3530, 3456, 3171, 3051, 2858, 2760, 1665, 1616, 1401, 1295, 1269, 1220, 1072, 1043, 825, 778, 741, 690 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.04 (1H, d, *J* 9.5 Hz, C*H*), 7.47 (1H, t, *J* 7.8 Hz, C*H*), 7.74 (1H, t, *J* 7.8 Hz, C*H*), 7.88 (1H, d, *J* 7.8 Hz, C*H*), 8.07 (1H, d, *J* 7.8 Hz, C*H*), 8.33 (1H, d, *J* 9.5 Hz, C*H*), 13.30 (2H, br s, N*H*); δ_C (50 MHz, DMSO-d_6) 110.2, 118.2, 121.6, 125.4, 128.8, 132.5, 135.6, 142.5, 150.8.

*4.3.4. 4-Methylquinolinium-2-ylamino sulfate (**9**).* A white solid (1.63 g, 64%), mp 228 °C dec; [Found C, 47.17; H, 4.22; N, 10.81. $C_{10}H_{10}N_2O_4S$ requires C, 47.24; H, 3.96; N, 11.02]; ν_{max} (KBr) 3160, 3074, 2973, 2934, 2884, 1666, 1613, 1299, 1263, 1248, 1231, 1057, 845, 766, 736, 618 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 2.63 (3H, s, CH_3),

6.89 (1H, s, C*H*), 7.48–7.55 (1H, m, C*H*), 7.73–7.80 (1H, m, C*H*), 7.97 (1H, d, *J* 8.0 Hz, C*H*), 8.10 (1H, d, *J* 8.0 Hz, C*H*), 13.20 (2H, br s, N*H*); δ_C (50 MHz, DMSO-d_6) 19.3, 108.9, 118.8, 122.1, 125.6 (two signals), 132.5, 135.6, 150.6, 152.3.

*4.3.5. Isoquinolinium-1-ylamino sulfate (**10**).* A white solid (1.42 g, 59%), mp 207–210 °C; [Found C, 44.88; H, 3.49; N, 11.38. $C_9H_8N_2O_4S$ requires C, 45.00; H, 3.36; N, 11.66]; ν_{max} (KBr) 3164, 3076, 2922, 1655, 1622, 1606, 1551, 1490, 1376, 1307, 1256, 1234, 1212, 1067, 1007, 799, 706, 614 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 7.29 (1H, d, *J* 7.0 Hz, C*H*), 7.63–7.98 (4H, m, C*H*), 8.43 (1H, d, *J* 7.0 Hz, C*H*), 12.97 (2H, br s, N*H*); δ_C (50 MHz, DMSO-d_6) 112.6, 115.3, 124.8, 127.9, 128.0, 129.1, 134.9, 136.7, 150.6.

4.4. General procedure for the formation of (4-pyrimidylamino)-diazopyrimidines 11, 11a, and 12

Compound **6** or **7** (0.01 mol) was dissolved in a 10% aqueous solution of K_2CO_3 (25 mL) and the reaction mixture was left at room temperature for 6 days. The red-colored solid that precipitated was collected by filtration and purified by crystallization from DMF (compound **11**) or by preparative TLC using Chromatotron (**12**). Crystals of **11a** suitable for X-ray analysis were obtained by slow evaporation of the solution of equimolar amounts of **11** (0.28 g, 1 mmol) and imidazole (68 mg, 1 mmol) in methanol/water (2:1).

*4.4.1. N-(2-(Pyrimidin-2-yldiazenyl)pyrimidin-5-yl)pyrimidin-2-amine (**11**).* An orange solid (0.28 g, 30%), mp 234–236 °C; [Found C, 51.50; H, 3.51; N, 44.87. $C_{12}H_9N_9$ requires C, 51.61; H, 3.25; N, 45.14]; ν_{max} (KBr) 3415, 3252, 3166, 3079, 3017, 1606, 1569, 1528, 1499, 1450, 1419, 1392, 1211, 821 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.08 (1H, t, *J* 4.9 Hz, C*H*), 7.71 (1H, t, *J* 4.9 Hz, C*H*), 8.66 (2H, d, *J* 4.9 Hz, C*H*), 9.07 (2H, d, *J* 4.9 Hz, C*H*), 9.46 (2H, s, C*H*), 10.58 (1H, s, N*H*); δ_C (125 MHz, DMSO-d_6) 115.1, 122.8, 137.6, 147.7, 159.2, 159.8, 160.1, 160.6, 167.8.

*4.4.2. N-(2-(Pyrimidin-2-yldiazenyl)pyrimidin-5-yl)pyrimidin-2-amine x imidazole (**11a**).* A red solid (0.26 g, 76%), mp 247–250 °C; ν_{max} (KBr) 3449, 3177, 3117, 3078, 2932, 1629, 1568, 1525, 1495, 1447, 1422, 1381, 1258, 1206, 1078 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.00 (2H, br s, C*H*), 7.08 (1H, t, *J* 4.9 Hz, C*H*), 7.62 (1H, s, C*H*), 7.71 (1H, t, *J* 4.9 Hz, C*H*), 8.66 (2H, d, *J* 4.9 Hz, C*H*), 9.07 (2H, d, *J* 4.9 Hz, C*H*), 9.46 (2H, s, C*H*), 10.58 (1H, s, N*H*), 12.00 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 115.1, 122.8, 135.8, 137.6, 147.7, 159.2, 159.8, 160.1, 160.6, 167.8.

*4.4.3. 4-Methoxy-N-(4-methoxy-2-((4-methoxypyrimidin-2-yl)diazenyl)pyrimidin-5-yl)pyrimidin-2-amine (**12**).* An orange solid (0.41 g, 33%), mp 175–178 °C; [Found C, 48.72; H, 4.33; N, 33.85. $C_{15}H_{15}N_9O_3$ requires C, 48.78; H, 4.09; N, 34.13]; R_f (AcOEt) 0.22; ν_{max} (KBr) 3421, 2951, 1584, 1562, 1527, 1488, 1423, 1405, 1376, 1331, 1193, 1021 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.02 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 4.26 (3H, s, OCH_3), 6.35 (1H, d, *J* 5.8 Hz, C*H*), 6.82 (1H, d, *J* 5.8 Hz, C*H*), 7.66 (1H, br s, N*H*), 8.23 (1H, d, *J* 5.8 Hz, C*H*), 8.62 (1H, d, *J* 5.8 Hz, C*H*), 9.93 (1H, s, C*H*); δ_C (50 MHz, $CDCl_3$) 54.7, 55.0, 55.7, 101.7, 109.1, 124.7, 143.6, 158.1, 158.8, 159.0, 159.1, 159.5, 167.5, 171.0, 171.6.

4.5. General procedure for the reactions of heteroaromatic hydroxylamine-*O*-sulfonates with acyl isothiocyanates

A suspension of corresponding heteroarylinium-ylamino sulfate **6**–**10** (2.5 mmol) in DMF (3 mL) was treated with triethylamine (0.35 mL, 2.5 mmol) at room temperature and the resulting mixture was stirred until a clear solution was obtained (ca. 2 min). Then, the suitable acyl isothiocyanate was added and stirring was continued until the slightly exothermic reaction had subsided (ca. 10 min) Upon treatment of the reaction mixture with a second equivalent of triethylamine (0.35 mL, 2.5 mmol), the desired product precipitated. Compounds **13**–**19**, **21**–**24**, or **26** thus obtained were collected by suction, washed with DMF and purified by crystallization from DMF. Compounds **20** and **25**, which are soluble in DMF were isolated upon quenching the reaction mixture with water (5 mL) followed by extraction with methylene chloride (2×5 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The oily residue thus obtained was purified on silica with use of Chromatotron (CH_2Cl_2).

*4.5.1. N-(2H-[1,2,4]Thiadiazolo[2,3-a]pyrimidin-2-ylidene)benzamide (**13**).* A white solid (0.34 g, 53%), mp 260 °C dec (lit. 24 mp 230 °C); [Found C, 56.01; H, 3.32; N, 21.57. $C_{12}H_8N_4OS$ requires C, 56.24; H, 3.15; N, 21.86]; ν_{max} (KBr) 3107, 3055, 1605, 1534, 1522, 1479, 1452, 1438, 1381, 1349, 1174, 939, 714, 682 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 7.48 (1H, dd, ^3J=6.3 Hz, ^3J=4.5 Hz, C*H*), 7.54–7.67 (3H, m, C*H*), 8.24–8.28 (2H, m, C*H*), 9.12 (1H, dd, ^3J=4.5 Hz, ^4J=2.1 Hz, C*H*), 9.44 (1H, dd, ^3J=6.3 Hz, ^4J=2.1 Hz, C*H*); δ_C (125 MHz, CF_3COOH/C_6D_6) 116.8, 129.0, 129.7, 135.5, 137.2, 144.2, 156.7, 164.1, 170.4, 170.8.

*4.5.2. N-(2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-ylidene)acetamide (**14**).* A white solid (0.09 g, 19%), mp 220 °C dec; [Found C, 42.97; H, 3.37; N, 28.63. $C_7H_6N_4OS$ requires C, 43.29; H, 3.11; N, 28.85]; ν_{max} (KBr) 3103, 3054, 3032, 2995, 1607, 1533, 1488, 1456, 1375, 1337, 1257, 1020, 997, 808, 788, 732, 684 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 2.27 (3H, s, CH_3), 6.98 (1H, t, *J* 5.0 Hz, C*H*), 8.28 (1H, d, *J* 5.0 Hz, C*H*), 8.70 (1H, d, *J* 5.0 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 20.1, 117.2, 144.9, 157.6, 164.4, 169.8, 177.0.

*4.5.3. Ethyl 2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-ylidenecarbamate (**15**).* A white solid (0.21 g, 37%); mp 238–240 °C (lit. 26 mp 237–240 °C); [Found C, 42.56; H, 3.93; N, 24.69. $C_8H_8N_4O_2S$ requires C, 42.85; H, 3.60; N, 24.99]; ν_{max} (KBr) 3083, 2987, 1593, 1531, 1481, 1455, 1406, 1382, 1367, 1329, 1302, 1227, 1210, 1126, 1074, 912, 816, 788 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.29 (3H, t, *J* 7.0 Hz, CH_3), 4.27 (2H, q, *J* 7.0 Hz, CH_2), 7.38–7.40 (1H, m, C*H*), 9.03–9.04 (1H, m, C*H*), 9.35–9.37 (1H, m, C*H*); δ_C (50 MHz, CF_3COOH) 12.8, 68.6, 116.8, 144.9, 156.8, 158.6, 164.5, 172.7.

*4.5.4. N-(5-methoxy-2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-ylidene)benzamide (**16**).* A white solid (0.30 g, 42%), mp 250–253 °C; [Found C, 54.48; H, 3.63; N, 19.39. $C_{13}H_{10}N_4O_2S$ requires C, 54.54; H, 3.52; N, 19.57]; ν_{max} (KBr) 3091, 3064, 2954, 1610, 1522, 1506, 1447, 1355, 1257, 1028, 976, 777, 720 cm^{-1}; δ_H (500 MHz, CF_3COOD) 3.93 (3H, s, OCH_3), 6.73 (1H, d, *J* 6.8 Hz, C*H*), 7.31 (2H, t, *J* 7.0 Hz, C*H*), 7.48 (1H, t, *J* 7.0 Hz, C*H*), 7.88 (2H, d, *J* 7.0 Hz, C*H*), 8.48 (d, *J* 6.8 Hz, 1H, C*H*); δ_C (125 MHz, CF_3COOD) 57.5, 109.3, 126.6, 130.2, 131.0, 138.2, 142.9, 160.2, 171.9, 173.1, 174.6.

*4.5.5. N-(5-methoxy-2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-ylidene)acetamide (**17**).* A white solid (0.09 g, 16%), mp 221 °C dec; [Found C, 42.77; H, 3.84; N, 24.80. $C_8H_8N_4O_2S$ requires C, 42.85; H, 3.60; N, 24.99]; ν_{max} (KBr) 3092, 3051, 3001, 2949, 1624, 1531, 1514, 1412, 1378, 1275, 1267, 1042, 1000, 823, 776 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 2.25 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.47 (1H, d, *J* 7.0 Hz, C*H*), 7.78 (1H, d, *J* 7.0 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 20.2, 56.6, 108.2, 141.5, 158.8, 170.6, 173.2, 176.2.

*4.5.6. Ethyl 5-methoxy-2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-ylidenecarbamate (**18**).* A white solid (0.23 g, 36%), mp 214–215 °C; [Found C, 42.46; H, 4.06; N, 21.97. $C_9H_{10}N_4O_3S$ requires C, 42.51; H, 3.96; N, 22.03]; ν_{max} (KBr) 3093, 2984, 2914, 1626, 1593, 1544, 1519, 1497, 1441, 1374, 1333, 1270, 1256, 1223, 1072, 1010, 970, 824,

787 cm^{-1}; δ_H (500 MHz, CF_3COOH/C_6D_6) 1.27 (3H, t, *J* 7.0 Hz, C*H*$_3$), 3.97 (3H, s, OC*H*$_3$), 4.35 (2H, q, *J* 7.0 Hz, C*H*$_2$), 6.56 (1H, d, *J* 7.3 Hz, C*H*), 7.93 (1H, d, *J* 7.3 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 12.7, 56.4, 68.1, 107.7, 141.3, 156.1, 159.6, 172.9, 173.2.

*4.5.7. N-(2H-[1,2,4]thiadiazolo[2,3-a]quinolin-2-ylidene)benzamide (**19**).* A white solid (0.25 g, 33%), mp 283–285 °C; [Found C, 67.01; H, 3.97; N, 13.80. $C_{17}H_{11}N_3OS$ requires C, 66.87; H, 3.63; N, 13.76]; ν_{max} (KBr) 3067, 2923, 1615, 1587, 1518, 1474, 1446, 1399, 1337, 1295, 1275,1221, 1163, 1122, 899, 750, 722, 701 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.58 (2H, t, *J* 7.3 Hz, C*H*), 7.65 (1H, t, *J* 7.3 Hz, C*H*), 7.70 (1H, t, *J* 7.8 Hz, C*H*), 7.85 (1H, d, *J* 9.0 Hz, C*H*), 7.95 (1H, t, *J* 7.8 Hz, C*H*), 8.18 (1H, d, *J* 7.8 Hz, C*H*), 8.28 (2H, d, *J* 7.3 Hz, C*H*), 8.34 (1H, d, *J* 7.8 Hz, C*H*), 8.53 (1H, d, *J* 9.0 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 116.0, 118.0, 126.0, 126.4, 129.6, 130.2, 130.5, 131.3, 135.3, 135.6, 137.5, 144.4, 154.9, 169.1, 170.1.

*4.5.8. N-(2H-[1,2,4]thiadiazolo[2,3-a]quinolin-2-ylidene)acetamide (**20**).* A white solid (0.05 g, 8%), mp 230 °C dec; [Found C, 59.08; H, 3.87; N, 16.99. $C_{12}H_9N_3OS$ requires C, 59.24; H, 3.73; N, 17.27]; R_f (AcOEt) 0.57; ν_{max} (KBr) 3048, 1630, 1546, 1506, 1423, 1381, 1361, 1340, 982, 815, 746, 701 cm^{-1}; δ_H (500 MHz, CF_3COOH/C_6D_6) 2.19 (3H, s, C*H*$_3$), 7.06 (1H, d, *J* 6.8 Hz, C*H*), 7.27 (1H, d, *J* 6.8 Hz, C*H*), 7.51 (1H, d, *J* 7.8 Hz, C*H*), 7.56–7.59 (2H, m, C*H*), 7.61–7.64 (2H, m, C*H*), 8.43 (1H, d, *J* 7.8 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 20.5, 121.1, 122.7, 124.3, 126.6, 128.0, 131.5, 135.8, 136.0, 155.8, 166.9, 175.2.

*4.5.9. Ethyl 2H-[1,2,4]thiadiazolo[2,3-a]quinolin-2-ylidenecarbamate (**21**).* A white solid (0.20 g, 30%), mp 208–213 °C; [Found C, 56.89; H, 4.34; N, 15.20. $C_{13}H_{11}N_3O_2S$ requires C, 57.13; H, 4.06; N, 15.37]; ν_{max} (KBr) 3028, 2976, 2926, 1592, 1576, 1494, 1448, 1410, 1368, 1317, 1274, 1194, 1078, 832, 789, 754 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 1.25 (3H, t, *J* 7.2 Hz, C*H*$_3$), 4.29 (2H, q, *J* 7.2 Hz, C*H*$_2$), 7.17 (1H, d, *J* 9.0 Hz, C*H*), 7.32–7.60 (4H, m, C*H*), 7.86 (1H, d, *J* 9.0 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 13.2, 67.8, 116.2, 117.7, 125.1, 129.6, 130.9, 134.7, 135.0, 143.6, 156.0, 156.5, 170.3.

*4.5.10. N-(5-methyl-2H-[1,2,4]thiadiazolo[2,3-a]quinolin-2-ylidene) benzamide (**22**).* A white solid (0.42 g, 52%), mp 295 °C dec; [Found C, 67.71; H, 4.29; N, 13.19. $C_{18}H_{13}N_3OS$ requires C, 67.69; H, 4.10; N, 13.16]; ν_{max} (KBr) 3093, 2984, 2914, 1626, 1593, 1544, 1519, 1497, 1441, 1374, 1333, 1270, 1256, 1223, 1072, 1010, 970, 824, 787 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 2.34 (3H, s, C*H*$_3$), 7.11–7.65 (7H, m, C*H*), 7.66–7.70 (1H, m, C*H*), 8.02–8.08 (2H, m, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 19.3, 115.9, 118.2, 125.7, 126.4, 127.3, 129.4, 129.5, 130.3, 134.3, 134.6, 137.1, 154.0, 155.0, 168.3, 169.5.

*4.5.11. Ethyl 5-methyl-2H-[1,2,4]thiadiazolo[2,3-a]quinolin-2-ylidenecarbamate (**23**).* A white solid (0.33 g, 46%), mp 207–213 °C dec; [Found C, 58.31; H, 4.88; N, 14.63. $C_{14}H_{13}N_3O_2S$ requires C, 58.52; H, 4.56; N, 14.62]; ν_{max} (KBr) 3062, 2985, 2932, 1618, 1566, 1523, 1488, 1454, 1406, 1367, 1321, 1291, 1253, 1222, 1092, 1076, 790, 750 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 1.28 (3H, t, *J* 7.2 Hz, C*H*$_3$), 2.46 (3H, s, C*H*$_3$), 4.32 (2H, q, *J* 7.2 Hz, C*H*$_2$), 7.29–7.31 (2H, m, C*H*), 7.51–7.66 (2H, m, C*H*), 7.76–7.80 (1H, m, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 13.1, 19.0, 67.8, 116.0, 118.2, 125.5, 127.3, 129.5, 134.2, 134.7, 155.2, 155.8, 155.9, 170.3.

*4.5.12. N-(2H-[1,2,4]thiadiazolo[3,2-a]isoquinolin-2-ylidene)benzamide (**24**).* A white solid (0.44 g, 58%), mp 283–285 °C; [Found C, 66.74; H, 3.77; N, 13.65. $C_{17}H_{11}N_3OS$ requires C, 66.87; H, 3.63; N, 13.76]; ν_{max} (KBr) 3110, 3056, 1630, 1523, 1503, 1445, 1379, 1355, 1237, 1129, 925, 797, 719, 695, 687 cm^{-1}; δ_H (500 MHz, CF_3COOH/C_6D_6) 7.27–7.35 (1H, m, C*H*), 7.39–7.46 (2H, m, C*H*), 7.53–7.62 (2H, m, C*H*), 7.66–7.72 (2H, m, CH), 7.73–7.79 (1H, m, C*H*), 7.98–8.04 (2H, m, C*H*), 11.37 (1H, d, *J* 7.8 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 121.1, 122.1, 124.2, 125.9, 126.1, 128.0, 129.0, 129.9, 131.4, 135.7, 136.1, 136.7, 155.2, 168.3, 169.8.

*4.5.13. N-(2H-[1,2,4]thiadiazolo[3,2-a]isoquinolin-2-ylidene)acetamide (**25**).* A white solid (0.09 g, 15%), mp 248 °C dec; [Found C, 58.89; H, 4.02; N, 17.00. $C_{12}H_9N_3OS$ requires C, 59.24; H, 3.73; N, 17.27]; R_f (AcOEt) 0.57; ν_{max} (KBr) 3102, 3048, 2923, 2853, 1630, 1545, 1506, 1423, 1381, 1361, 1340, 982, 815, 746, 701 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 2.29 (3H, s, C*H*$_3$), 7.25 (1H, d, *J* 7.0 Hz, C*H*), 7.49 (1H, d, *J* 7.0 Hz, C*H*), 7.63–7.77 (3H, m, C*H*), 8.51 (1H, d, *J* 7.8 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 20.3, 121.1, 122.7, 124.3, 126.6, 128.0, 131.5, 135.8, 136.0, 158.8, 166.9, 175.2.

*4.5.14. Ethyl 2H-[1,2,4]thiadiazolo[3,2-a]isoquinolin-2-ylidenecarbamate (**26**).* A white solid (0.43 g, 63%), mp 233–235 °C; [Found C, 57.10; H, 4.29; N, 15.08. $C_{13}H_{11}N_3O_2S$ requires C, 57.13; H, 4.06; N, 15.37]; ν_{max} (KBr) 3052, 2988, 2919, 1630, 1579, 1562, 1513, 1393, 1378, 1361, 1329, 1241, 1222, 1131, 1112, 1086, 805, 747, 696 cm^{-1}; δ_H (200 MHz, CF_3COOH/C_6D_6) 1.27 (3H, t, *J* 7.2 Hz, C*H*$_3$), 4.32 (2H, q, *J* 7.2 Hz, C*H*$_2$), 7.21 (1H, d, *J* 7.1 Hz, C*H*), 7.45 (1H, d, *J* 7.1 Hz, C*H*), 7.61–7.75 (3H, m, C*H*), 8.45 (1H, d, *J* 8.1 Hz, C*H*); δ_C (50 MHz, CF_3COOH/C_6D_6) 13.0, 67.7, 120.8, 122.6, 124.4, 126.8, 128.0, 131.5, 135.9, 136.0, 156.2, 157.5, 170.2.

Supplementary data

General experimental details; crystallographic data; Cartesian coordinates, computed electronic energies, and Gibbs free energies for structures **A**, **E**, **F**, **G** and **15** along with relative energies reported in the paper; exemplary ^1H NMR, ^{13}C NMR, and IR spectra for compounds **8**, **16**, **19**, and **20**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.091.

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