Biaryl Sulfonamides from *O*-Acetyl Amidoximes: 1,2,4-Oxadiazole Cyclization under Acidic Conditions

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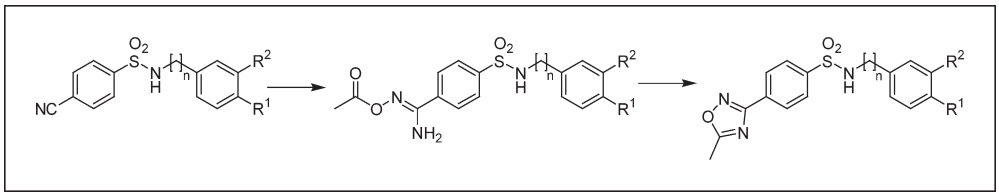

A series of 4-cyanobenzenesulfonamides (**1a–h**) was converted to the corresponding *O*-acetylated amidoximes (**2a–h**). The reaction of **1a** was exemplarily investigated with respect to the formation of a byproduct, which was identified as 1,2,4-oxadiazole derivative **3a**. This observation led to the development of an improved procedure for the preparation of **2a–h**. Compounds **2** could be transformed to 1,2,4-oxadiazoles **3a–h** in high yields and purity upon heating in acetic acid.

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INTRODUCTION

The 1,2,4-oxadiazole heterocycle has been found in a large number of compounds which display biological activity. Among a series of 5-alkyl-1,2,4-oxadiazol-3-yl-benzenesulfonamides, a 5-*n*-pentyl derivative was a particularly potent β_3 adrenergic receptor agonist [1]. The 1,2,4-oxadiazole moiety has been incorporated in selective SH2 inhibitors of tyrosine kinase ZAP-70 [2], novel 5-HT_3 antagonists [3], and histamine H_3 receptor antagonists [4].

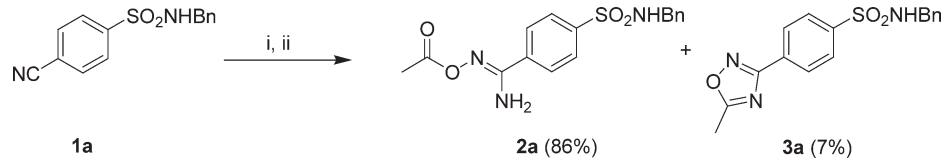
Because of their increased hydrolytic stability, oxadiazoles are often considered as ester bioisosteres in drug discovery research. For example, replacement of the methyl esters in arecoline or azabicyclo derivatives by 3- and 5-methyl-1,2,4-oxadiazole resulted in potent muscarinic agonists [5,6]. As benzodiazepine-receptor ligands, oxadiazoles have also been found to be metabolically stable alternatives to esters [7–9], and oxadiazoles related to disoxaril with antirhinoviral activity were identified [10]. The use of 1,2,4-oxadiazoles as amide mimetics has frequently been reported, for example to improve the *in vivo* efficacy of benzodiazepine receptor ligands [11] and to develop new inhibitors of palmitoyl-CoA oxidation [12]. The carboxamide-oxadiazole replacement led to A_{2B}-selective xanthine-based adenosine receptor antagonist [13] and to rimonabant-related CB1 cannabinoid-receptor antagonists [14]. Moreover, 1,2,4-oxadiazoles have been reported as dipeptidomimetics and successfully used in the design of pseudopeptides as μ- and δ-opioid and NK_1 receptor ligands [15,16].

The typical synthetic route to 1,2,4-oxadiazoles includes the *O*-acylation of easily accessible amidoximes [17], followed by their intramolecular condensation. For the first step, acid chlorides [18], esters [19], or symmetrical anhydrides [15] have been used, or carboxylic acids have been coupled to amidoximes in the presence of CDI, DCC, EDC, or BOP-Cl [20,21]. The 1,2,4-oxadiazoles were then obtained after thermal condensation of the *O*-acylated amidoxime precursors [22]. Numerous conditions for the dehydration step have been published, mostly involving heating in solvents such as DMF [23,24], diglyme [20], pyridine [15], or water [25]. Sodium acetate-catalyzed cyclodehydration was performed to produce series of enantiopure 1,2,4-oxadiazole-containing, Fmoc-protected β^3- and α-amino acids [26,27]. Cyclization could also proceed at room temperature, provided the presence of a strong basic reagent like TBAF [28]. Direct cyclization has also been reported, for example when reacting benzamidoxime with succinic anhydride under solvent-free conditions [29] or with acyl chlorides in pyridine [30]. However, da Costa Leite et al. heated aryl amidoximes in acetic acid as solvent and observed a product mixture of 3,5-bis(aryl)-1,2,4-oxadiazoles and 3-aryl-5-methyl-1,2,4-oxadiazoles [31].

RESULTS AND DISCUSSION

In the course of our studies related to the inhibition of serine proteases, we have designed benzamidines containing a sulfonamide structure as amide bioisostere

Scheme 1. Conditions: (i) $H_2NOH \times HCl$, DIPEA, EtOH, 87°C, 1 h; (ii) Ac_2O (3 equiv), AcOH, room temperature, 1 h.



1a **2a** (86%) **3a** (7%)

with strong hydrogen bonding donor–acceptor properties [32,33]. To take advantage of the preference of trypsin-like enzymes for arginine, the benzamidine substructure was chosen as a well-known arginine mimetic [34,35]. Thus, we were interested in a straightforward synthesis of a library of benzamidines from carbonitriles, which includes the formation of amidoximes, their *O*-acetylation and final reduction. These three steps were analyzed with respect to side products to develop a one-pot procedure to benzamidines. The first two steps were combined and the representative sulfonamide-containing nitrile **1a** was reacted with hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine (DIPEA) in refluxing ethanol. The crude product was directly dissolved in acetic acid [36] and treated with acetic anhydride (Scheme 1). Monitoring the reaction by TLC, a second product with unexpected low polarity was observed. The byproduct was separated from the desired *O*-acetylated substance **2a** by column chromatography and was then recrystallized. NMR spectroscopy showed a downfield shift of the methyl protons of 0.54 ppm and an upfield shift of the methyl carbon of 7.7 ppm, relative to the signals of **2a**. The NH_2 resonance and the N═C─N carbon signal at 155.6 ppm disappeared, whereas a new signal at 178.1 ppm was observed. Finally, the structure was confirmed by X-ray crystallography [37] to be the dehydrated 1,2,4-oxadiazole **3a** (Fig. 1, Table 1).

The cyclodehydration of *O*-acylated amidoximes at room temperature in the absence of a base has not been described in literature yet. It was not possible to complete the dehydration of **2a**, neither by increasing the reaction time nor by operating at higher temperatures, which even led to decomposition. Therefore, suitable conditions should be established to (i) convert *O*-acetylated amidoximes **2** to corresponding 1,2,4-oxadiazoles **3** and (ii) produce the benzamidine precursors **2** free of heterocyclic impurities. The corresponding reactions are depicted in Scheme 2.

Upon reaction with different amines, in dichloromethane and the presence of pyridine [38], the commercially available 4-cyanobenzenesulfonyl chloride was converted to eight cyano-substituted sulfonamides **1a–h** (Table 2). The corresponding *O*-acetylated amidoximes **2a–h** were obtained in good yields (Table 2) by a procedure combining the reaction with hydroxylamine and the *O*-acetylation. When performing the acetylation at room temperature using three equivalents of acetic anhydride and acetonitrile as the solvent, instead of acetic

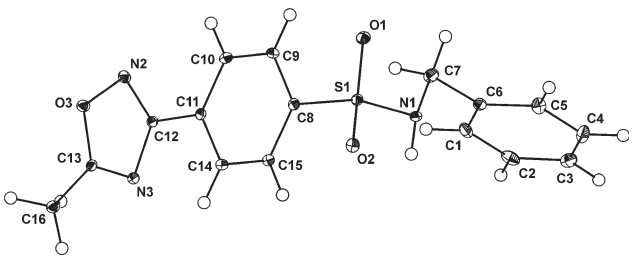


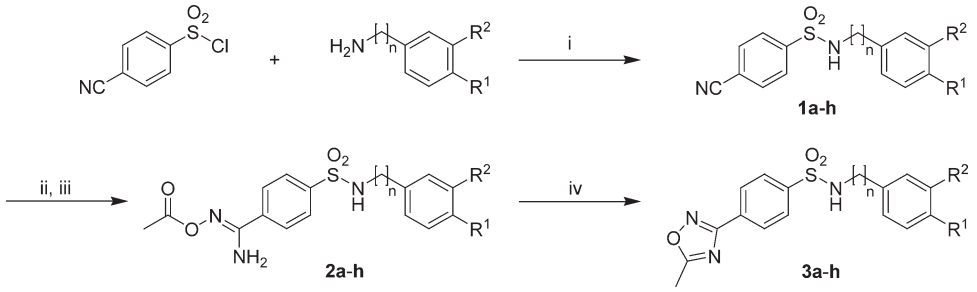
Figure 1. Molecular plot of **3a** showing the atom-labeling scheme and displacement ellipsoids at 30% probability level for the non-H atoms. H atoms are depicted as small circles of arbitrary radii [37].

Table 1

Crystallographic data of **3a.**

Empirical formula	$C_{16}H_{15}N_3O_3S$
Formula weight	329.37
Temperature	163(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 11.7210(3)$ Å; $\alpha = 105.463(2)°$ $b = 11.9411(2)$ Å; $\beta = 98.7490(10)°$ $c = 16.9507(5)$ Å; $\gamma = 92.208(2)°$
Volume	2252.16(10) $Å^3$
Z, Calculated density	6, 1.457 Mg/m^3
Absorption coefficient	0.235 mm^{-1}
F(000)	1032
Crystal size	0.42 mm × 0.33 mm × 0.19 mm
θ range for data collection	2.34–27.48°
Limiting indices	h, k, l −15/15, −15/15, −22/2
Reflections collected/unique	40076/10139 [R(int) = 0.0399]
Completeness to θ	98.1% ($\theta_{max} = 27.48°$)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9567 and 0.9078
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	10139/0/628
Goodness-of-fit on F^2	0.996
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0360$, $\omega R_2 = 0.0882$
R indices (all data)	$R_1 = 0.0563$, $\omega R_2 = 0.0956$
Largest diff. peak and hole	0.265 and −0.569 e/$Å^{-3}$

Scheme 2. Conditions: (i) pyridine, CH_2Cl_2, room temperature, 24 h; (ii) $H_2NOH \times HCl$, DIPEA, EtOH, 87°C, 1 h; (iii) Ac_2O (3 equiv), MeCN, room temperature, 1 h; (iv) AcOH, 80°C, 6 h.



acid, no heterocyclized byproducts were observed. The series of *O*-acetylated amidoximes **2** will be used for further transformation to benzamidines to become part of a library of potential serine protease inhibitors. Their biological evaluation is in progress and will be reported in due course.

The final 1,2,4-oxadiazoles **3a–h** were prepared from **2a**–**h** in acetic acid at 80°C (Table 2). Crystallization from ethyl acetate/hexane afforded the products in excellent purity. When compared with the initial experiment noted above, this procedure resulted in a complete conversion and yields of >78%. The use of purified material **2** in the cyclodehydration step seems favorable for the desired course of the reaction. An exemplary compound, **2a**, was cyclized in acetic acid at 120°C. This time, the product formation was completed after 1 h and the product, **3a**, was obtained in the same yield (80%) after recrystallization. The structural elucidation for **3a**–**h** was based on elemental analysis, ^{1}H- and ^{13}C-NMR data. Signals of both oxadiazole carbons, C-3 and C-5, appeared about 11 ppm downfield shifted, compared with the corresponding carbons in compounds **2**. Oxadiazole cyclizations, including the one presented herein, are useful methods for the introduction of heterocyclic biphenyl-analogous building blocks in the design of bioactive compounds, for example, inhibitors of cysteine cathepsins [39].

EXPERIMENTAL

Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany), Merck-Schuchardt (Hohenbrunn, Germany) or Sigma (Steinheim, Germany). Thin-layer chromatography was carried out on Merck aluminum sheets, silica gel 60 F_{254}. Preparative column chromatography was performed on Merck silica gel 60, 70–230 mesh. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts δ are given in ppm referring to the signal center using the solvent peak for reference: DMSO-d_6 2.49 ppm/39.7 ppm. The NMR signals were assigned by ^{1}H, ^{13}C correlation spectra (HMQC, HMBC) using standard pulse sequences. Elemental analyses were carried out with a Vario EL apparatus.

General procedure for the synthesis 4-cyanobenzenesulfonamides (1a–1h). A mixture of 4-cyanobenzenesulfonyl chloride (605 mg, 3 mmol), amine (3.3 mmol) and pyridine

Table 2

Conversion of 4-cyanobenzenesulfonamides to *O*-acetylated amidoximes and corresponding 1,2,4-oxadiazoles.

R^1	R^2	*n*	Nitrile	Yield (%)[a]	*O*-Acetyl-amidoxime	Yield (%)[a,b]	1,2,4-Oxadiazole	Yield (%)[a]
H	H	1	**1a**	71	**2a**	83	**3a**	80
OMe	H	1	**1b**	97	**2b**	77	**3b**	94
H	OMe	1	**1c**	67	**2c**	77	**3c**	84
OMe	OMe	1	**1d**	46	**2d**	91	**3d**	79
H	H	0	**1e**	45	**2e**	92	**3e**	87
OMe	H	0	**1f**	75	**2f**	75	**3f**	85
H	OMe	0	**1g**	92	**2g**	74	**3g**	90
OMe	OMe	0	**1h**	88	**2h**	95	**3h**	88

[a] Yields after recrystallization.
[b] No formation of 1,2,4-oxadiazole, monitored by TLC.

(736 mg, 9.3 mmol) was stirred for 24 h at room temperature in dry dichloromethane (10 mL). The solvent was removed under reduced pressure, acetic acid (1 mL) was added and the oily residue was purified by flash-column chromatography (dichloromethane). The product was obtained after recrystallization.

N-Benzyl-4-cyanobenzenesulfonamide (1a). Using benzylamine (354 mg, 3.3 mmol) as the amine component, the product **1a** was obtained following the general procedure after recrystallization from ethanol/water. Yield 580 mg (71%). Colorless solid, mp 138–140°C, ref. 40, 141–142°C; ^{1}H-NMR (DMSO-d_6): δ 4.04 (s, 2H, CH_2), 7.17–7.27 (m, 5H, phenyl-H), 7.90 (d, 2H, J = 8.8 Hz, phenyl-H), 8.01 (d, 2H, J = 8.8 Hz, phenyl-H), 8.45 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 46.3 (CH_2), 114.8 (C_q), 117.9 (CN), 127.4 (3× CH, Ph), 127.8 (2× CH, Ph), 128.4 (2× CH, Ph), 133.4 (2× CH, Ph), 137.3 (C_q), 145.2 (C_q).

4-Cyano-N-(4-methoxybenzyl)benzenesulfonamide (1b). Using 4-methoxybenzylamine (453 mg, 3.3 mmol), the product **1b** was obtained following the general procedure after recrystallization from toluene. Yield 880 mg (97%). Colorless solid, mp 128–131°C; ^{1}H-NMR (DMSO-d_6): δ 3.70 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.78 (d, 2H, J = 8.6 Hz, phenyl-H), 7.08 (d, 2H, J = 8.8 Hz, phenyl-H), 7.87 (d, 2H, J = 8.5 Hz, phenyl-H), 8.00 (d, 2H, J = 8.5 Hz, phenyl-H), 8.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 45.9 (CH_2), 55.2 (CH_3), 113.8 (2× CH, Ph), 114.7 (C_q), 117.9 (CN), 127.3 (2× CH, Ph), 129.1 (C_q), 129.2 (2× CH, Ph), 133.4 (2× CH, Ph), 145.3 (C_q), 158.7 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59%; H, 4.67%; N, 9.27%. Found C, 59.71%; H, 4.70%; N, 9.18%.

4-Cyano-N-(3-methoxybenzyl)benzenesulfonamide (1c). Using 3-methoxybenzylamine (453 mg, 3.3 mmol), the product **1c** was obtained after recrystallization from toluene. Yield 610 mg (67%). Colorless needles, mp 124–127°C; ^{1}H-NMR (DMSO-d_6): δ 3.67 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 6.71 (dd, 1H, J = 1.9 Hz, J = 1.9 Hz, phenyl-H), 6.74–6.77 (m, 2H, phenyl-H), 7.15 (dd, 1H, J = 7.9 Hz, J = 7.9 Hz, phenyl-H), 7.88 (d, 2H, J = 8.2 Hz, phenyl-H), 8.00 (d, 2H, J = 8.5 Hz, phenyl-H), 8.44 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 46.2 (CH_2), 55.1 (CH_3), 112.9, 113.3 (2× CH, Ph), 114.8 (C_q), 117.9 (CN), 119.9, 129.4, 127.3, 133.3 (6× CH, Ph), 138.8 (C_q), 145.2 (C_q), 159.3 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59%; H, 4.67%; N, 9.27%. Found C, 59.61%; H, 4.72%; N, 9.12%.

4-Cyano-N-(3,4-dimethoxybenzyl)benzenesulfonamide (1d). Using 3,4-dimethoxybenzylamine (552 mg, 3.3 mmol), the product **1d** was obtained following the general procedure after recrystallization from ethyl acetate/toluene. Yield 460 mg (46%). Pink solid, mp 171–175°C; ^{1}H-NMR (DMSO-d_6): δ 3.64, 3.69 (each s, 6H, CH_3), 3.98 (s, 2H, CH_2), 6.67 (dd, 1H, J = 8.2 Hz, J = 1.9 Hz, phenyl-H), 6.72 (d, 1H, J = 1.9 Hz, phenyl-H), 6.77 (d, 1H, J = 8.2 Hz, phenyl-H), 7.86 (d, 2H, J = 8.8 Hz, phenyl-H), 7.98 (d, 2H, J = 8.8 Hz, phenyl-H), 8.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 46.2 (CH_2), 55.5, 55.7 (CH_3), 111.7, 111.8 (2× CH, Ph), 114.7 (C_q), 117.9 (CN), 120.2, 127.4 (3× CH, Ph), 129.5 (C_q), 133.3 (2× CH, Ph), 145.3 (C_q), 148.2 (C_q), 148.7 (C_q). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82%; H, 4.85%; N, 8.43%. Found C, 57.99%; H, 4.86%; N, 8.34%.

4-Cyano-N-phenyl-benzenesulfonamide (1e). Using aniline (307 mg, 3.3 mmol), the product **1e** was obtained following the general procedure after recrystallization from ethyl acetate/hexane. Yield 349 mg (45%). White powder, mp 110–111°C; ^{1}H-NMR (DMSO-d_6): δ 7.03–7.09 (m, 3H, phenyl-H), 7.24 (dd, 2H, J = 8.7 Hz, J = 7.6 Hz, phenyl-H), 7.88 (d, 2H, J = 8.8 Hz, phenyl-H), 8.02 (d, 2H, J = 8.9Hz, phenyl-H), 10.49 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 115.5 (C_q), 117.7 (CN), 120.8, 124.8, 127.5, 129.4, 133.6 (9× CH, Ph), 137.1 (C_q), 143.7 (C_q). Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45%; H, 3.90%; N, 10.85%. Found C, 59.87%; H, 3.83%; N, 10.49%.

4-Cyano-N-(4-methoxyphenyl)benzenesulfonamide (1f). Using *p*-anisidine (406 mg, 3.3 mmol), the product **1f** was obtained following the general procedure after recrystallization from toluene. Yield 650 mg (75%). White powder, mp 148–149°C, ref. 41, 188–191°C; ^{1}H-NMR (DMSO-d_6): δ 3.66 (s, 3H, CH_3), 6.81 (d, 2H, J = 9.2 Hz, phenyl-H), 6.95 (d, 2H, J = 9.2 Hz, phenyl-H), 7.81 (d, 2H, J = 8.5 Hz, phenyl-H), 8.01 (d, 2H, J = 8.8 Hz, phenyl-H), 10.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.3 (CH_3), 114.6 (2× CH, Ph), 115.3 (C_q), 117.2 (CN), 124.1, 127.6 (4× CH, Ph), 129.4 (C_q), 133.5 (2× CH, Ph), 143.7 (C_q), 157.1 (C_q). Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32%; H, 4.20%; N, 9.72%. Found C, 58.48%; H, 4.32%; N, 9.65%.

4-Cyano-N-(3-methoxyphenyl)benzenesulfonamide (1g). Using *m*-anisidine (406 mg, 3.3 mmol), the product **1g** was obtained following the general procedure after recrystallization from toluene. Yield 800 mg (92%). Yellow crystals, mp 99–103°C; ^{1}H-NMR (DMSO-d_6): δ 3.66 (s, 3H, CH_3), 6.61–6.67 (m, 3H, phenyl-H), 7.13 (dd, 1H, J = 8.6 Hz, J = 8.4 Hz, phenyl-H), 7.90 (d, 2H, J = 8.9 Hz, phenyl-H), 8.03 (d, 2H, J = 8.8 Hz, phenyl-H), 10.50 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.2 (CH_3), 106.4, 109.9, 112.5 (3× CH, Ph), 115.5 (C_q), 117.7 (CN), 127.6, 130.3, 133.6 (5× CH, Ph), 138.4 (C_q), 143.6 (C_q), 159.9 (C_q). Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32%; H, 4.20%; N, 9.72%. Found C, 58.49%; H, 4.25%; N, 9.58%.

4-Cyano-N-(3,4-dimethoxyphenyl)benzenesulfonamide (1h). Using 4-aminoveratrole (505 mg, 3.3 mmol), the product **1h** was obtained following the general procedure after recrystallization from toluene. Yield 730 mg (76%). Dark pink crystals, mp 135–140°C; ^{1}H-NMR (DMSO-d_6): δ 3.63, 3.66 (each s, 6H, CH_3), 6.53 (dd, 1H, J = 8.7 Hz, J = 2.2 Hz, phenyl-H), 6.66 (d, 1H, J = 2.5 Hz, phenyl-H), 6.80 (d, 1H, J = 8.5 Hz, phenyl-H), 7.84 (d, 2H, J = 8.8 Hz, phenyl-H), 8.02 (d, 2H, J = 8.9 Hz, phenyl-H), 10.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 55.6, 55.87 (CH_3), 107.1, 112.2, 114.3 (3× CH, Ph), 115.3 (C_q), 117.7 (CN), 127.6 (2× CH, Ph), 129.8 (C_q), 133.5 (2× CH, Ph), 143.6 (C_q), 146.1 (C_q), 149.0 (C_q). Anal. Calcd. for $C_{15}H_{14}N_2O_4S$: C, 56.59%; H, 4.43%; N, 8.80%. Found C, 56.89%; H, 4.51%; N, 8.69%.

Conversion of 1a to a mixture of 2a and 3a. A mixture of *N*-benzyl-4-cyanobenzenesulfonamide **1a** (545 mg, 2 mmol), hydroxylamine-hydrochloride (278 mg, 4 mmol) and DIPEA (517 mg, 4.08 mmol) in dry ethanol (17 mL) was refluxed for 1 h. The solvent was removed and the oily residue was dissolved in acetic acid (8 mL). After addition of acetic anhydride (613 mg, 6 mmol), the solution was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 2:1) to obtain **2a** (598 mg, 86%) and **3a** (46 mg, 7%). Compound **3a** was recrystallized from ethyl acetate/hexane.

General procedure for the synthesis of *N*-acetoxy-benzimidamides (2a–2h). A mixture of hydroxylamine-hydrochloride (2 equiv) and the 4-cyanobenzenesulfonamide (1 equiv) was refluxed in ethanol (25 mL) in the presence of DIPEA (2 equiv) for 1 h. Afterward, the solvent was removed *in vacuo*. The residue was dissolved in acetonitrile (20 mL), and acetic anhydride (3 equiv) was added. After 1 h, the solvent was evaporated, and the *N*-acetoxy-benzimidamide was isolated after recrystallization from ethyl acetate/hexane as a colorless solid.

***N*-Acetoxy-4-(*N*′-benzylsulfamoyl)benzimidamide (2a).** Following the general procedure, product **2a** was afforded from **1a** (429 mg, 1.58 mmol). Yield 455 mg (83%). White solid, mp 168–170°C; ^{1}H-NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.95 (s, 2H, NH_2), 7.20–7.30 (m, 5H, phenyl-H), 7.86 (d, J = 8.8 Hz, 2H, phenyl-H), 7.89 (d, J = 8.8 Hz, 2H, phenyl-H), 8.23 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.3 (CH_2), 126.7, 127.3, 127.7, 127.7, 128.4 (9× CH), 135.4 (C_q), 137.7 (C_q), 142.5 (C_q), 155.6 (N═C─N), 168.5 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.32%; H, 4.93%; N, 12.10%. Found C, 55.03%; H, 5.28%; N, 11.71%.

***N*-Acetoxy-4-(*N*′-(4-methoxybenzyl)sulfamoyl)benzimidamide (2b).** Following the general procedure, product **2b** was afforded from **1b** (756 mg, 2.5 mmol). Yield 727 mg (77%). Colorless solid, mp 165–166°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2), 6.82 (d, J = 8.9 Hz, 2H, phenyl-H), 6.94 (s, 2H, NH_2), 7.13 (d, J = 8.6 Hz, 2H, phenyl-H), 7.83 (d, J = 8.8 Hz, 2H, phenyl-H), 7.88 (d, J = 8.9 Hz, 2H, phenyl-H), 8.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 45.8 (CH_2), 55.2 (OCH_3), 113.8, 126.6, 127.6, 129.1 (8× CH, Ph), 129.4 (C_q), 135.3 (C_q), 142.5 (C_q), 155.6 (N═C─N), 158.6 (C_q), 168.4 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_5S$: C, 54.10%; H, 5.07%; N, 11.13%. Found C, 53.97%; H, 5.13%; N, 11.07%.

***N*-Acetoxy-4-(*N*′-(3-methoxybenzyl)sulfamoyl)benzimidamide (2c).** Following the general procedure, product **2c** was afforded from **1c** (346 mg, 1.14 mmol). Yield 333 mg (77%). White solid, mp 118–120°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2), 6.77–6.81 (m, 3H, phenyl-H), 6.94 (s, 2H, NH_2), (7.18 (dd, J = 7.6 Hz, J = 8.8 Hz, 1H, phenyl-H), 7.85 (d, J = 8.5 Hz, 2H, phenyl-H), 7.89 (d, J = 8.6 Hz, 2H, phenyl-H), 8.22 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.2 (CH_2), 55.1 (OCH_3), 112.9, 113.1, 119.8, 126.7, 127.7, 129.5 (8× CH, Ph), 135.4 (C_q), 129.2 (C_q), 142.5 (C_q), 155.5 (N═C─N), 159.4 (C_q), 168.5 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_5S$: C, 54.10%; H, 5.07%; N, 11.13%. Found C, 54.06%; H, 5.16%; N, 10.89%.

***N*-Acetoxy-4-(*N*′-(3,4-dimethoxybenzyl)sulfamoyl)benzimidamide (2d).** Following the general procedure, product **2d** was afforded from **1d** (341 mg, 1.03 mmol). Yield 380 mg (91%). White solid, mp 137–138°C; ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.65, 3.69 (each s, 6H, OCH_3), 3.93 (s, 2H, CH_2), 6.72 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H, phenyl-H), 6.76 (d, J = 1.9 Hz, 1H, phenyl-H), 6.81 (d, J = 8.2 Hz, 1H, phenyl-H), 6.93 (s, 2H, NH_2), 7.83 (d, J = 8.9 Hz, 2H, phenyl-H), 7.88 (d, J = 8.5 Hz, 2H, phenyl-H), 8.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 46.2 (CH_2), 55.5, 55.7 (OCH_3), 111.7, 111.8, 120.0, 126.7, 127.6 (7× CH, Ph), 129.8 (C_q), 135.4 (C_q), 142.6 (C_q), 148.2 (C_q), 148.7 (C_q), 155.5 (N═C─N), 168.5 (CO). Anal. Calcd. for $C_{18}H_{21}N_3O_6S$: C, 53.06%; H, 5.20%; N, 10.31%. Found C, 53.00%; H, 5.29%; N, 10.05%.

***N*-Acetoxy-4-(*N*′-phenylsulfamoyl)benzimidamide (2e).** Following the general procedure, product **2e** was afforded from **1e** (280 mg, 1.08 mmol). Yield 333 mg (92%). Colorless needles, mp 166–167°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 6.91 (s, 2H, NH_2), 7.02 (tt, 1H, J = 7.4 Hz, J = 1.0 Hz, phenyl-H), 7.01–7.11 (m, 2H, phenyl-H), 7.22 (dd, 2H, J = 7.6 Hz, J = 8.5 Hz, phenyl-H), 7.80, (d, J = 8.9 Hz, 2H, phenyl-H), 7.84 (d, 2H, J = 8.5 Hz, phenyl-H), 10.33 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 120.4, 124.4, 126.9, 127.8, 129.3 (9× CH, Ph), 135.9 (C_q), 137.6 (C_q), 141.3 (C_q), 155.5 (N═C─N), 168.4 (CO). Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.04%; H, 4.54%; N, 12.60%. Found C, 54.01%; H, 4.57%; N, 12.37%.

***N*-Acetoxy-4-(*N*′-(4-methoxyphenyl)sulfamoyl)benzimidamide (2f).** Following the general procedure, product **2f** was afforded from **1f** (625 mg, 2.17 mmol). Yield 590 mg (75%). White crystalline solid, mp 150–152°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.80 (d, J = 9.2 Hz, 2H, phenyl-H), 6.91 (s, 2H, NH_2), 6.97 (d, J = 9.2 Hz, 2H, phenyl-H), 7.72 (d, J = 8.6 Hz, 2H phenyl-H), 7.83 (d, J = 8.8 Hz, 2H, phenyl-H), 9.96 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.3 (OCH_3), 114.5, 123.8, 126.9, 127.7 (8× CH, Ph), 129.9 (C_q), 135.7 (C_q), 141.2 (C_q), 155.5 (N═C─N), 156.8 (C_q), 168.4 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88%; H, 4.72%; N, 11.56%. Found C, 52.67%; H, 4.79%; N, 11.38%.

***N*-Acetoxy-4-(*N*′-(3-methoxyphenyl)sulfamoyl)benzimidamide (2g).** Following the general procedure, product **2g** was afforded from **1g** (641 mg, 2.22 mmol). Yield 600 mg (74%). White solid, mp 120–121°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 6.60 (ddd, J = 8.5 Hz, J = 2.4 Hz, J = 0.6 Hz, 1H, phenyl-H), 6.65–6.67 (m, 2H, phenyl-H), 6.91 (s, 2H, NH_2), 7.12 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, phenyl-H), 7.82 (d, J = 8.5 Hz, 2H, phenyl-H), 7.85 (d, J = 8.8 Hz, 2H, phenyl-H), 10.35 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.1 (OCH_3), 106.0, 109.4, 112.2, 126.9, 127.8, 130.2 (8× CH, Ph), 136.0 (C_q), 138.8 (C_q), 141.2 (C_q), 155.5 (N═C─N), 159.8 (C_q), 168.4 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88%; H, 4.72%; N, 11.56%. Found C, 52.48%; H, 4.75%; N, 11.40%.

***N*-Acetoxy-4-(*N*′-(3,4-dimethoxyphenyl)sulfamoyl)benzimidamide (2h).** Following the general procedure, product **2h** was afforded from **1h** (430 mg, 1.35 mmol). Yield 504 mg (95%). White crystalline solid, mp 116–118°C; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.63 (each s, 6H, OCH_3), 6.54 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, phenyl-H), 6.69 (d, J = 2.2 Hz, 1H, phenyl-H), 6.79 (d, J = 8.5 Hz, 1H, phenyl-H), 6.91 (s, 2H, NH_2), 7.76 (d, J = 8.5 Hz, 2H, phenyl-H), 7.84 (d, J = 8.5 Hz, 2H, phenyl-H), 9.97 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 19.9 (CH_3), 55.6, 55.7 (OCH_3), 106.9, 112.3, 113.9, 127.0, 127.7 (7× CH, Ph), 130.4 (C_q), 135.8 (C_q), 141.2 (C_q), 146.4 (C_q), 149.0 (C_q), 155.5 (N═C─N), 168.4 (CO). Anal. Calcd. for $C_{17}H_{19}N_3O_6S$: C, 51.90%; H, 4.87%; N, 10.68%. Found C, 50.73%; H, 5.17%; N, 10.38%.

General procedure for the preparation of 1,2,4-oxadiazoles (3a–3h). Compound **2** was stirred in acetic acid (15 mL) for 6 h at 80°C. The solvent was removed under reduced pressure, and the corresponding 1,2,4-oxaziazole was obtained after recrystallization from ethyl acetate/hexane.

N-Benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3a). Following the general procedure, compound **3a** was prepared from **2a** (348 mg, 1.0 mmol). Yield 263 mg (80%). Colorless solid, mp 158–159°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 7.17–7.28 (m, 5H, phenyl-H), 7.94 (d, 2H, J = 8.6 Hz, phenyl-H), 8.14 (d, J = 8.5 Hz, 2H, phenyl-H), 8.32 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.3 (CH_2), 127.3, 127.5, 127.7, 127.8, 128.3 (9× CH, Ph), 129.7 (C_q), 137.6 (C_q), 143.5 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.34%; H, 4.59%; N, 12.76%. Found C, 58.41%; H, 4.75%; N, 13.01%.

N-(4-Methoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3b). Following the general procedure, compound **3b** was prepared from **2b** (377 mg, 1.0 mmol). Yield 338 mg (94%). Colorless solid, mp 152–153°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.96 (d, J = 6.3 Hz, 2H, CH_2), 6.79 (d, J = 8.5 Hz, 2H, phenyl-H), 7.12 (d, J = 8.5 Hz, 2H, phenyl-H), 7.92 (d, J = 8.9 Hz, 2H, phenyl-H), 8.14 (d, J = 8.9 Hz, 2H, phenyl-H), 8.22 (t, J = 6.3 Hz, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 45.9 (CH_2), 55.2 (OCH_3), 113.8, 127.5, 127.8, 129.1 (8× CH, Ph), 129.4 (C_q), 129.7 (C_q), 143.5 (C_q), 158.6 (C_q), 166.9 (N═C─N), 178.1 (O─C═N). Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81%; H, 4.77%; N, 11.69%. Found C, 56.83%; H, 4.77%; N, 11.49%.

N-(3-Methoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3c). Following the general procedure, compound **3c** was prepared from **2c** (199 mg, 527 μmol). Yield 160 mg (84%). Colorless solid, mp 152–154°C; ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.03 (d, J = 6.0 Hz, 2H, CH_2), 6.73–6.80 (m, 3H, phenyl-H), 7.15 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.0 Hz, 1H, phenyl-H), 7.93 (d, J = 8.6 Hz, 2H, phenyl-H), 8.12 (d, J = 8.5 Hz, 2H, phenyl-H), 8.31 (t, J = 6.0 Hz, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.2 (CH_2), 55.1 (OCH_3), 112.9, 113.1, 119.9, 127.5, 127.8, 129.4 (8× CH, Ph), 129.7 (C_q), 139.1 (C_q), 143.5 (C_q), 159.3 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81%; H, 4.77%; N, 11.69%. Found C, 56.70%; H, 4.78%; N, 11.39%.

N-(3,4-Dimethoxybenzyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl) benzenesulfonamide (3d). Following the general procedure, compound **3d** was prepared from **2d** (390 mg, 957 μmol). Yield 294 mg (79%). Colorless solid, mp 170–171°C; ^{1}H-NMR (DMSO-d_6): δ 2.68 (s, 3H, CH_3), 3.63, 3.66 (each s, 6H, OCH_3), 3.98 (s, 2H, CH_2), 6.71 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H, phenyl-H), 6.75 (d, J = 1.9 Hz, 1H, phenyl-H), 6.78 (d, J = 8.2 Hz, 1H, phenyl-H), 7.91 (d, J = 8.5 Hz, 2H, phenyl-H), 8.12 (d, J = 8.8 Hz, 2H, phenyl-H), 8.22 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 46.2 (CH_2), 55.4, 55.7 (OCH_3), 111.7, 111.8, 120.0, 127.5, 127.7 (7× CH, Ph), 129.6 (C_q), 129.7 (C_q), 143.5 (C_q), 148.2 (C_q), 148.7 (C_q), 166.9 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{18}H_{19}N_3O_5S$: C, 55.52%; H, 4.92%; N, 10.97%. Found C, 55.34%; H, 5.14%; N, 10.46%.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-phenyl-benzenesulfonamide (3e). Following the general procedure, compound **3e** was prepared from **2e** (382 mg, 1.15 mmol). Yield 315 mg (87%). Colorless solid, mp 175–176°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.03 (tt, J = 7.6 Hz, 1.3 Hz, 1H, phenyl-H), 7.08–7.10 (m, 2H, phenyl-H), 7.22 (dd, J = 7.3 Hz, J = 8.6 Hz, 2H, phenyl-H), 7.91 (d, J = 8.8 Hz, 2H, phenyl-H), 8.13 (d, J = 8.8 Hz, 2H, phenyl-H), 10.38 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 120.6, 124.6, 127.8, 128.0, 129.4 (9× CH, Ph), 130.3 (C_q), 137.5 (C_q), 142.1 (C_q), 166.8 (N═C─N), 178.2 (N═C─O). Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13%; H, 4.16%; N, 13.33%. Found C, 57.22%; H, 4.28%; N, 13.09%.

N-(4-Methoxyphenyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3f). Following the general procedure, compound **3f** was prepared from **2f** (190 mg, 523 μmol). Yield 154 mg (85%). Colorless solid, mp 174–177°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.80 (d, J = 9.2 Hz, 2H, phenyl-H), 6.97 (d, J = 9.2 Hz, 2H, phenyl-H), 7.83 (d, J = 8.5 Hz, 2H, phenyl-H), 8.12 (d, J = 8.2 Hz, 2H, phenyl-H), 10.01 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.3 (OCH_3), 114.5, 124.0, 127.8, 127.8 (8× CH, Ph), 129.8 (C_q), 130.1 (C_q), 142.0 (C_q), 156.9 (C_q), 166.8 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64%; H, 4.38%; N, 12.17%. Found C, 55.52%; H, 4.37%; N, 12.06%.

N-(3-Methoxyphenyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (3g). Following the general procedure, compound **3g** was prepared from **2g** (406 mg, 1.12 mmol). Yield 350 mg (90%). Colorless solid, mp 162–164°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.59–6.61 (m, 1H, phenyl-H), 6.67–6.68 (m, 2H, phenyl-H), 7.12 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, phenyl-H), 7.93 (d, J = 8.2 Hz, 2H, phenyl-H), 8.14 (d, J = 8.5 Hz, 2H, phenyl-H), 10.40 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.2 (OCH_3), 106.2, 109.6, 112.4, 127.8, 128.0, 130.2 (8× CH, Ph), 130.3 (C_q), 138.7 (C_q), 142.0 (C_q), 159.9 (C_q), 166.7 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64%; H, 4.38%; N, 12.17%. Found C, 55.88%; H, 4.38%; N, 12.06%.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-(3,4-dimethoxyphenyl)-benzenesulfonamide (3h). Following the general procedure, compound **3h** was prepared from **2h** (490 mg, 1.25 mmol). Yield 411 mg (88%). Brown crystals, mp 186–187°C; ^{1}H-NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 3.62, 3.65 (s, 6H, OCH_3), 6.55 (dd, J = 8.5 Hz, J = 2.5 Hz, 1H, phenyl-H), 6.68 (d, J = 2.2 Hz, 1H, phenyl-H), 6.97 (d, J = 8.9 Hz, 1H, phenyl-H), 7.86 (d, J = 8.5 Hz, 2H, phenyl-H), 8.13 (d, J = 8.9 Hz, 2H, phenyl-H), 10.02 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, APT): δ 12.2 (CH_3), 55.6, 55.7 (OCH_3), 107.1, 112.2, 114.2, 127.8, 127.9 (7× CH, Ph), 130.2 (C_q), 130.2 (C_q), 142.0 (C_q), 146.6(C_q), 149.0 (C_q), 166.8 (N═C─N), 178.1 (N═C─O). Anal. Calcd. for $C_{17}H_{17}N_3O_5S$: C, 54.39%; H, 4.56%; N, 11.19%. Found C, 54.21%; H, 4.70%; N, 10.99%.

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[37] CCDC 763842 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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