



Cite this: *RSC Adv.*, 2020, 10, 26701

Received 22nd May 2020
Accepted 12th June 2020

DOI: 10.1039/d0ra04545d

rsc.li/rsc-advances

Transition metal- and catalyst-free one-pot green method for the synthesis of *N*-sulfonyl amidines via direct reaction of sulfonyl azides with amines†

Babak Kaboudin,^a Saeed Torabi,^a Foad Kazemi^a and Hiroshi Aoyama^b

In this report, a green synthesis of *N*-sulfonyl amidines via the direct reaction of tertiary or secondary amines with sulfonyl azides is described. Transition metal- and catalyst-free conditions were used for the synthesis of biologically important *N*-sulfonyl amidines. Further studies showed that the reaction proceeded *via in situ* aerobic oxidation of amines under reflux conditions.

Introduction

Amidines with N=C=N bonds are known compounds in nature with an important role in pharmaceuticals and strong coordination affinity toward metal ions.^{1–4} Among the amidine compounds, *N*-sulfonyl amidines are of interest as they are effective in medicinal chemistry and synthesis of synthetic intermediates for drugs.^{5–12} A number of *N*-sulfonyl amidines with medicinal and biochemical applications are shown in Scheme 1. These compounds are bioactive pharmacophores with inhibitors of dopamine transporter,⁶ anti tumour,⁷ anti-bone resorptive agent⁸ and anti-proliferative⁹ properties (Fig. 1).

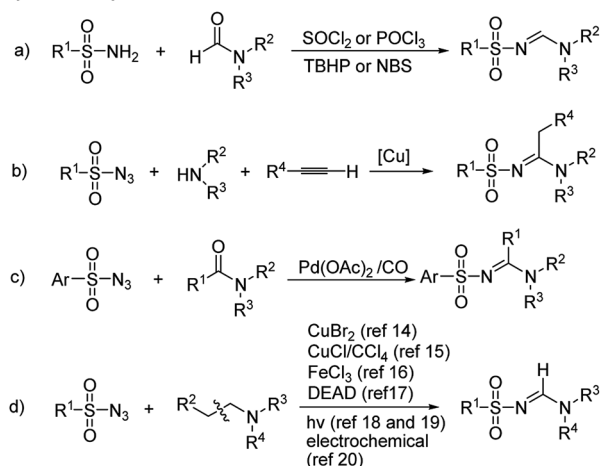
In the past years, various methods have been developed for the synthesis of *N*-sulfonyl amidines.^{13–21} These include: (a) condensation of amides with sulfonylamides,^{13,14} (b) Cu-catalyzed three-component coupling reactions of sulfonyl azides, alkynes and secondary amines,¹⁵ (c) Pd-catalyzed carbonylation/coupling of sulfonylazides and substituted amides,¹⁶ and (d) cross-coupling reaction of sulfonyl azides with tertiary amines^{17–21} (Scheme 1). Among them, cross-coupling of sulfonyl azides with tertiary amines has attracted much more attention. The key intermediate is enamine generated by oxidative dehydrogenation of amines in the presence of CuBr₂,¹⁷ CuCl/CCl₄,¹⁸ or FeCl₃.¹⁹ On the other hand, Li and co-workers reported the cascade reaction of tertiary amines with sulfonyl azides in the presence of DEAD (diethyl azodicarboxylate) for the preparation of *N*-sulfonyl amidines.²⁰

Recently, photocatalyzed cross-coupling of arylsulfonyl azides with tertiary amines in the presence of eosin Y and

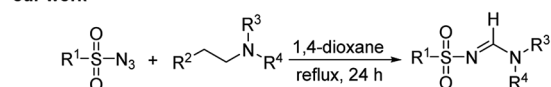
acridinium salts have been reported by Zeng *et al.*²¹ and Pan *et al.*²² respectively. An electrochemical synthesis of *N*-sulfonyl amidines from aliphatic amines and sulfonyl azides has been reported by Wang, Du and Zah.²³ Syntheses of *N*-sulfonyl amidines based on the reaction between the sulfonyl azides and amines require harsh reaction conditions and stoichiometric or catalytic amounts of transition metal catalysts. Therefore, the development of an efficient, green, and novel method for the synthesis of *N*-sulfonyl amidines is thus highly desirable.

Recently we have reported catalyst-free synthesis of alkylaminophenols *via* Petasis-type reaction²⁴ and decarboxylative P–C coupling reaction of amino acids.²⁵ In continuation of our efforts in developing new green synthetic methods, herein we

previous reports



our work



Scheme 1 Previously reported works and our work.

^aDepartment of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Gava Zang, Zanjan, 45137-66731, Iran. E-mail: kaboudin@gmail.com; Tel: +98 24 3315 3220

^bSchool of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Horinouchi, Hachioji, Tokyo 192-0392, Japan

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra04545d



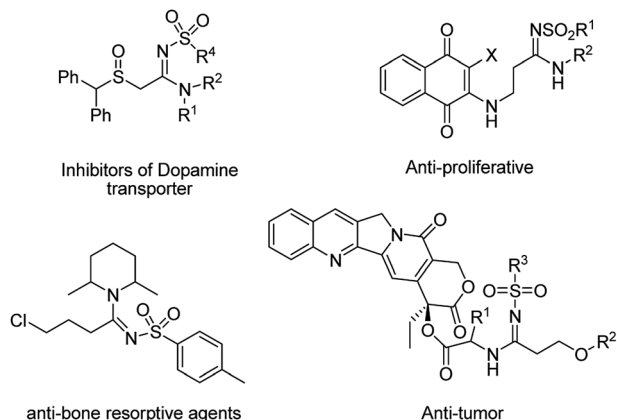


Fig. 1 Structures of biological active *N*-sulfonyl amidines.

report an efficient, practical, and high yielding catalyst-free synthesis of *N*-sulfonylamidines *via* the direct reaction of tertiary or secondary amines with sulfonyl azides.

Results and discussion

The cascade reaction of *p*-tosylazide (**1a**) with triethyl amine (**2a**) was chosen as the model reaction and screening results listed in

Table 1 Screening of various reaction condition for the preparation of compound **3a**

CC(C)N(CC)CC + S(=O)(=O)N=[N+]#N >> CC(C)N(CC)C(=O)N(S(=O)(=O)c1ccc(C)cc1)

Entry	Solvent (2 mL)	T (°C)	Ratio of		Time (h)	Yield ^a (%)
			1a	2a		
1	DMSO	rt	1 : 1	24	— ^b	
2	DMSO	110	1 : 1	24	35	
3	CHCl ₃	Reflux	1 : 1	24	55	
4	THF	Reflux	1 : 1	24	51	
5	Toluene	Reflux	1 : 1	24	62	
6	EtOH	Reflux	1 : 1	24	40	
7	CH ₃ CN	Reflux	1 : 1	24	61	
8	1,4-Dioxane	Reflux	1 : 1	24	66	
9	1,4-Dioxane	Reflux	1 : 1.5	24	69	
10	1,4-Dioxane	Reflux	1 : 2	24	71	
11	1,4-Dioxane	Reflux	1 : 2	24	— ^c	
12	1,4-Dioxane	Reflux	2 : 1	24	25	
13	1,4-Dioxane	rt	1 : 2	48	— ^b	
14	1,4-Dioxane	60	1 : 2	48	— ^b	
15	1,4-Dioxane	80	1 : 2	48	54	
16	1,4-Dioxane	Reflux	1 : 2	48	71	
17	1,4-Dioxane	Reflux	1 : 2	24	68 ^d	
18	1,4-Dioxane	Reflux	1 : 2	24	71 ^e	

^a Yields refers to the isolated pure products after short column chromatography. ^b No reaction. ^c Reaction under Ar or N₂. ^d Reaction in the presence of TEMPO (1 equiv.). ^e Reaction in the presence of dioxygen.

Table 1. Initially, no reaction was observed when DMSO was used as a solvent at room temperature for 24 h (entry 1). Upon heating the reaction mixture, the compound **3a** was obtained in 35% yield after 24 h at reflux condition (entry 2). The results for the reactions conducted in various solvents showed that using 1,4-dioxane as a solvent, the compound **3a** was obtained in 66% isolated yield (entries 3–8). When the reaction was conducted with 2 eq. of the amine **2a**, the compound **3a** was obtained in 71% yield (entry 10). No reaction was observed when the reaction conducted under Ar or N₂ atmosphere at reflux for 24 h (entry 11). With 2 : 1 ratio of azide to amine, the compound **3a** was obtained in 25% yield (entry 12). The reaction afforded **3a** in good yield at a reflux condition (entries 13–16). When the reaction was conducted in the presence of TEMPO (1 eq.), the compound **3a** was obtained in 68% yield (entry 17). The reaction afforded **3a** in 71% yield (same aerobic condition) in the presence of dioxygen at reflux condition (entry 18).

This result showed that the reaction mixture has no any radical intermediate under reaction condition. Therefore, further optimization on the amount of *p*-tosylazide (**1a**) and triethyl amine showed that treatment of azide **1a** with 2 equiv. of triethyl amine for 24 h produced *p*-tosylamide **3a** in 71% yield (entries 9–18).

Under the optimized conditions, a wide range of sulfonyl azides were employed in the cascade reaction with tertiary amines for the synthesis of *N*-sulfonylamidines in good to modest yields as shown in Table 2. The arylsulfonyl azides bearing electron-donating and electron-withdrawing groups reacted with triethylamine to afford the corresponding *N*-sulfonylamidines in moderate to good yields (**3a–3e**). The steric hindrance did not apply considerable influence on the reaction. 2,4,6-Trimethyl-benzenesulfonyl azide reacted smoothly with triethyl amine **2a** and the corresponding *N*-sulfonylamidines **3e** was obtained in 70% yield.

The aliphatic sulfonyl azides, camphorsulfonyl azide and methylsulfonyl azide, afforded the corresponding *N*-sulfonylamidines **3f** and **3g** in 63% and 71% isolated yields respectively. Furthermore, the reaction of arylsulfonyl azides with tri-propyl and tributyl amines afforded corresponding *N*-sulfonylamidines (**3h–3l**) in moderate to good yield (entries 8–12). Tertiary amines with different alkyl groups, *N,N*-diisopropylethylamine and *N,N*-diethyl aniline, were also investigated and the corresponding *N*-sulfonylamidines were obtained for each tertiary amine in good yields (entries 13–16). The cascade reaction of DABCO as a cyclic tertiary amine with *p*-methylphenylsulfonyl azide gave a mixture of unknown products (entry 17).

Interestingly, the corresponding sulfonamide **4** was obtained in 46% yield with using triethanol amine (Scheme 2). This experiment showed the product was obtained by the conversion of triethanol amine to its secondary amine followed by a nucleophilic substitution under optimized reaction condition.

In other attempt, a one-pot three component reaction of sulfonyl chloride **5a** with sodium azide (2 equiv.) and triethyl amine (2 equiv.) for the synthesis of *N*-sulfonylamidines was examined. The compound **3a** was obtained in 78% yield in 1,4-dioxane at reflux for 24 h (Scheme 3).



Table 2 The reaction of sulfonyl azides with tertiary amines for the preparation of *N*-sulfonylamidines

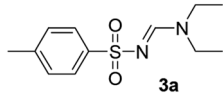
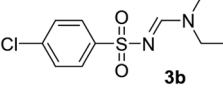
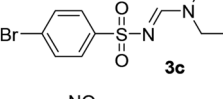
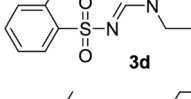
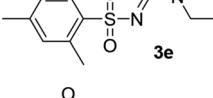
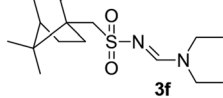
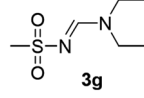
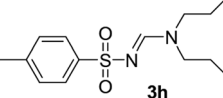
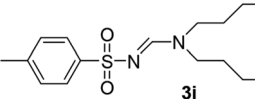
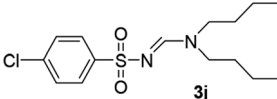
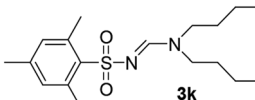
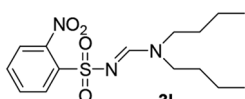
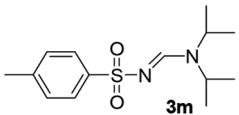
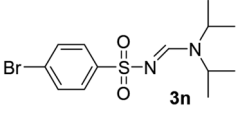
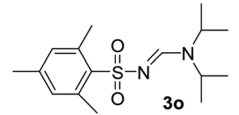
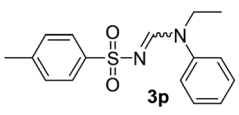
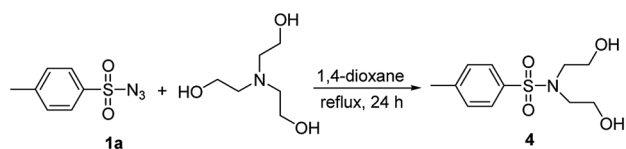
$ \begin{array}{c} \text{R}^1-\text{S}(=\text{O})_2-\text{N}_3 \\ \text{1} \end{array} + \begin{array}{c} \text{R}^2-\text{CH}_2-\text{CH}_2-\text{N}(\text{R}^3)\text{R}^4 \\ \text{2} \end{array} \xrightarrow[\text{reflux, 24 h}]{\text{1,4-dioxane}} \begin{array}{c} \text{R}^1-\text{S}(=\text{O})_2-\text{N}=\text{CH}-\text{N}(\text{R}^3)\text{R}^4 \\ \text{3} \end{array} $						
Entry	R ¹	R ²	R ³	R ⁴	Product 3	Yield ^a (%)
1	<i>p</i> -MeC ₆ H ₄ -	H	Et	Et	 3a	71
2	<i>p</i> -ClC ₆ H ₄ -	H	Et	Et	 3b	77
3	<i>p</i> -BrC ₆ H ₄ -	H	Et	Et	 3c	68
4	<i>o</i> -NO ₂ C ₆ H ₄ -	H	Et	Et	 3d	54
5	2,4,6-Me ₃ C ₆ H ₂ -	H	Et	Et	 3e	70
6	Camphoryl	H	Et	Et	 3f	63
7	Me-	H	Et	Et	 3g	71
8	<i>p</i> -MeC ₆ H ₄ -	Me	<i>n</i> -Pr	<i>n</i> -Pr	 3h	69
9	<i>p</i> -MeC ₆ H ₄ -	Et	<i>n</i> -Bu	<i>n</i> -Bu	 3i	58
10	<i>p</i> -ClC ₆ H ₄ -	Et	<i>n</i> -Bu	<i>n</i> -Bu	 3j	50
11	2,4,6-Me ₃ C ₆ H ₂ -	Et	<i>n</i> -Bu	<i>n</i> -Bu	 3k	46
12	<i>o</i> -NO ₂ C ₆ H ₄ -	Et	<i>n</i> -Bu	<i>n</i> -Bu	 3l	42



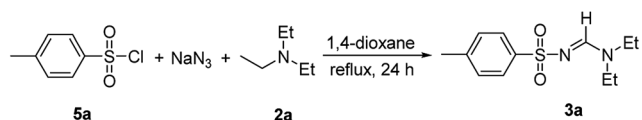
Table 2 (Contd.)

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{S}-\text{N}_3 \\ \parallel \\ \text{O} \end{array} + \begin{array}{c} \text{R}^3 \\ \\ \text{R}^2-\text{CH}_2-\text{CH}_2-\text{N}-\text{R}^4 \\ \\ \text{R}^3 \end{array} \xrightarrow[\text{reflux, 24 h}]{\text{1,4-dioxane}} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{S}-\text{N}=\text{CH}-\text{N}-\text{R}^4 \\ \parallel \\ \text{O} \end{array} $						
Entry	R ¹	R ²	R ³	R ⁴	Product 3	Yield ^a (%)
13	<i>p</i> -MeC ₆ H ₄ -	H	<i>i</i> -Pr	<i>i</i> -Pr		73
14	<i>p</i> -BrC ₆ H ₄ -	H	<i>i</i> -Pr	<i>i</i> -Pr		66
15	2,4,6-Me ₃ C ₆ H ₂ -	H	<i>i</i> -Pr	<i>i</i> -Pr		66
16	<i>p</i> -MeC ₆ H ₄ -	H	Et	Ph		48 ^b
17	<i>p</i> -MeC ₆ H ₄ -	—	—	—	—	— ^c

^a Yields refers to the isolated pure products after short column chromatography. ^b Mixture of *E* and *Z* configurations. ^c Mixture of unknown compounds in the presence DABCO.



Scheme 2 Reaction of 1a with triethanol amine in 1,4-dioxane.



Scheme 3 One pot reaction of 5a with triethylamine and sodium azide in 1,4-dioxane.

In order to find the activity of secondary amines, diethylamine 6a was attempted to be employed in the reaction with sulfonyl azide 1a in dioxane at reflux for 24 h. Interestingly, the compound 3a was obtained in 83% yield as found for the triethylamine. A series of sulfonyl azides were used to react with secondary amines 6 to provide the same products as found for the tertiary amines (Table 3) with moderate to good yields.

According to the literature reports and control experiments (Table 1, entries 10 and 16), a proposed mechanism was

outlined in Scheme 4. Initially, the cascade reaction was started *via* aerobic oxidation–dehydration of C–H bond adjacent to nitrogen atom of tertiary amines. Then, the formed enamine I was reacted with sulfonyl azide 1 to yield the unstable cyclic compound II. Finally *N*-sulfonylamidine 3 was obtained by a retro cycloaddition of the compound II. With secondary amines, the reaction proceeded by the enamine I formation *via* a known conversion of diethylamine to enamine I (Scheme 4).¹⁴

Conclusion

In summary, we report a green synthesis of *N*-sulfonyl amidines *via* the direct reaction of tertiary or secondary amines with sulfonyl azides. Under transition metal- and catalyst-free condition, aromatic and aliphatic *N*-sulfonyl azides could be converted into *N*-sulfonyl amidines in modest to good yields. The reported method is easy to handle, readily available starting materials, air and moisture insensitive reagents, and a simple method compared with previously reported methods.

Experimental section

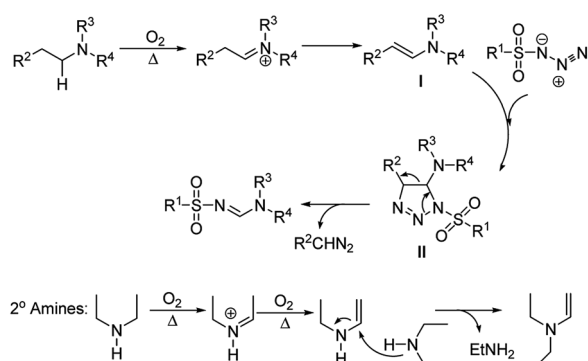
General

NMR spectra were obtained on a 400 and 250 MHz NMR Spectrometer (¹H NMR: 400 and 250 MHz and ¹³C NMR: 100 and 63 MHz). HRMS measurements were obtained on an ESI-



Table 3 The reaction of sulfonyl azides with secondary amines for the synthesis of *N*-sulfonylamidines^a

$\text{R}^1\text{-SO}_2\text{-N}_3 + \text{H}-\text{N}(\text{R}^2)_2 \xrightarrow[\text{reflux, 24 h}]{1,4\text{-dioxane}} \text{R}^1\text{-SO}_2\text{-N}=\text{N}-\text{N}(\text{R}^2)_2$		
1	6	3

^a Yields refers to the isolated pure products after short column chromatography.**Scheme 4** Proposed mechanism for the synthesis of compound 3.

TOF-MS machine. Analytical TLC was carried out with plates pre-coated with silica gel 60 F₂₅₄ (0.25 mm thick). Column chromatography was performed either with silica gel 60 (70–230 mesh) in common glass columns. All solvents were distilled before use.

General procedure for the synthesis of *N*-sulfonyl amidines from sulfonyl azides

Sulfonyl azide (1 mmol) was added to a solution of amine (2 mmol) in 1,4-dioxane (2 mL). The mixture was stirred for 24 h at reflux (oil bath at 110 °C) without using any inert gas under air. Water (5 mL) was added to the reaction mixture and the mixture was washed with ethyl acetate (3 × 5 mL) and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by a short column chromatography with *n*-hexane–EtOAc (7 : 3) to give compound 3 as the yellow viscous oil or

white solid (the reaction was also examined with 5 mmol of sulfonyl azide of 1a with triethyl amine and a similar yield of 3a was obtained).

(*E*)-*N*'-((4-Methylphenyl)sulfonyl)-*N,N*-diethylformimidamide (3a)¹⁷

Yellow oil (198 mg, 78% direct method from sulfonyl chloride); ¹H NMR (400 MHz, CDCl₃) δ: 8.17 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 2H), 3.40 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.1, 142.3, 139.7, 129.3, 126.4, 47.1, 40.9, 21.5, 14.5, 12.1; HRMS (ESI): calcd for C₁₂H₁₉N₂O₂S [M + H]⁺: 255.1167, found: 255.1151.

(*E*)-*N*'-((4-Chlorophenyl)sulfonyl)-*N,N*-diethylformimidamide (3b)¹⁷

Yellow oil (211 mg, 77%); ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 3.41 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.1, 141.2, 138.0, 128.9, 127.9, 47.2, 41.1, 14.5, 12.1.

(*E*)-*N*'-((4-Bromophenyl)sulfonyl)-*N,N*-diethylformimidamide (3c)²²

Light yellow solid (216 mg, 68%); ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 3.40 (q, *J* = 7.3 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.2, 141.7, 131.9, 128.0, 126.5, 47.2, 41.1, 14.5, 12.1.



(*E*)-*N'*-((2-Nitrophenyl)sulfonyl)-*N,N*-diethylformimidamide (3d)¹⁷

Yellow oil (154 mg, 54%); ¹H NMR (400 MHz, CDCl₃) δ: 8.31 (d, *J* = 8.3 Hz, 1H), 8.13 (s, 1H), 7.75–7.64 (m, 3H), 3.45–3.55 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 159.9, 147.7, 135.4, 132.7, 132.4, 130.7, 124.0, 47.4, 41.3, 14.4, 12.1.

(*E*)-*N'*-((2,4,6-Trimethylphenyl)sulfonyl)-*N,N*-diethylformimidamide (3e)²⁶

White solid (199 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ: 8.16 (s, 1H), 6.94 (s, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 3.38 (q, *J* = 7.3 Hz, 2H), 2.71 (s, 6H), 2.31 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.4, 141.1, 138.4, 136.6, 131.4, 46.8, 40.8, 23.0, 20.9, 14.6, 12.1.

(*E*)-*N'*-(((7,7-Dimethylbicyclo[2.2.1]hept-2-en-1-yl)methyl)sulfonyl)-*N,N*-diethylformimidamide (3f)²²

Colorless viscous oil (192 mg, 61%); ¹H NMR (400 MHz, CDCl₃) δ: 8.00 (s, 1H), 3.51–3.31 (m, 4H), 3.02–2.88 (m, 1H), 2.59 (ddd, *J* = 14.8, 11.4, 4.0 Hz, 1H), 2.40–2.19 (m, 1H), 2.09–1.94 (m, 2H), 1.86 (d, *J* = 18.3 Hz, 1H), 1.69 (ddd, *J* = 13.9, 9.2, 4.5 Hz, 1H), 1.44–1.29 (m, 2H), 1.29–1.02 (m, 9H), 0.82 (d, *J* = 3.0 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 215.3, 158.7, 58.5, 50.6, 48.0, 46.9, 42.7, 42.6, 40.7, 27.0, 24.7, 19.9, 19.7, 14.5, 12.0.

(*E*)-*N'*-(Methanesulfonyl)-*N,N*-diethylformimidamide (3g)¹⁹

Colorless viscous oil (126 mg, 71%); ¹H NMR (250 MHz, chloroform-*d*) δ: 8.05 (s, 1H), 3.47 (q, *J* = 7.2 Hz, 2H), 3.37 (q, *J* = 7.3 Hz, 2H), 2.94 (s, 3H), 1.29–1.22 (m, 3H), 1.22–1.14 (m, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 155.1, 44.0, 39.0, 37.8, 11.5, 9.0.

(*E*)-*N'*-((4-Methylphenyl)sulfonyl)-*N,N*-dipropylformimidamide (3h)¹⁷

Yellow viscous oil (195 mg, 69%); ¹H NMR (250 MHz, chloroform-*d*) δ: 8.13 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 3.33 (t, *J* = 7.8 Hz, 2H), 3.24 (t, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.58 (dd, *J* = 14.6, 7.3 Hz, 4H), 0.86 (dt, *J* = 14.1, 7.4 Hz, 6H); ¹³C{¹H} NMR (63 MHz, CDCl₃) δ: 155.9, 139.2, 136.8, 126.3, 123.3, 51.3, 44.8, 18.9, 18.5, 16.9, 8.2, 7.9.

(*E*)-*N'*-((4-Methylphenyl)sulfonyl)-*N,N*-dibutylformimidamide (3i)¹⁷

Yellow oil (171 mg, 55%); ¹H NMR (400 MHz, CDCl₃) δ: 8.16 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.42 (t, *J* = 7.4, 2H), 3.31 (t, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 1.62–1.50 (m, 4H), 1.25–1.35 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.7, 142.2, 139.8, 129.2, 126.3, 52.3, 46.0, 30.7, 28.7, 21.5, 20.0, 19.7, 13.7, 13.6.

(*E*)-*N'*-((4-Chlorophenyl)sulfonyl)-*N,N*-dibutylformimidamide (3j)¹⁷

Yellow oil (165 mg, 50%); ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 3.41 (t, *J* = 7.6 Hz, 2H), 3.32 (t, *J* = 7.4 Hz, 2H), 1.63–1.49 (m, 4H), 1.33–1.24 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.8, 141.3, 137.9, 128.9, 127.8, 52.4, 46.1, 30.7, 28.7, 19.9, 19.6, 13.7, 13.6.

(*E*)-*N'*-((2,4,6-Trimethylphenyl)sulfonyl)-*N,N*-diethylformimidamide (3k)²⁶

White solid (157 mg, 46%); ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (s, 1H), 6.93 (s, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.29 (t, *J* = 7.4 Hz, 2H), 2.70 (s, 6H), 2.31 (s, 3H), 1.61–1.51 (m, 4H), 1.35–1.29 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.9, 141.0, 138.3, 136.6, 131.4, 52.2, 46.1, 30.8, 28.7, 23.0, 20.9, 20.1, 19.6, 13.7, 13.6.

(*E*)-*N'*-((2-Nitrophenyl)sulfonyl)-*N,N*-diethylformimidamide (3l)¹⁷

Yellow oil (143 mg, 42%); ¹H NMR (400 MHz, CDCl₃) δ: 8.29–8.26 (m, 1H), 8.11 (s, 1H), 7.73–7.64 (m, 3H), 3.40 (m, 4H), 1.70–1.62 (m, 2H), 1.58–1.51 (m, 2H), 1.40–1.27 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 160.3, 147.7, 135.4, 132.7, 132.0, 130.7, 124.0, 52.7, 46.2, 30.6, 28.6, 19.8, 19.6, 13.6.

(*E*)-*N'*-((4-Methylphenyl)sulfonyl)-*N,N*-diisopropylformimidamide (3m)¹⁷

Yellow oil (206 mg, 73%); ¹H NMR (400 MHz, CDCl₃) δ: 8.26 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.53 (p, *J* = 6.8 Hz, 1H), 3.70 (p, *J* = 6.8 Hz, 1H), 2.41 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 156.4, 142.1, 139.9, 129.3, 126.2, 48.6, 47.9, 23.6, 21.5, 19.6.

(*E*)-*N'*-((4-Bromophenyl)sulfonyl)-*N,N*-diisopropylformimidamide (3n)²¹

White solid (228 mg, 66%); ¹H NMR (400 MHz, CDCl₃) δ: 7.76 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 4.54 (hept, *J* = 6.8 Hz, 1H), 3.73 (hept, *J* = 6.8 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 156.4, 141.9, 131.9, 127.9, 126.3, 48.8, 48.1, 23.6, 19.6.

(*E*)-*N'*-((2,4,6-Trimethylphenyl)sulfonyl)-*N,N*-diisopropylformimidamide (3o)²¹

White solid (205 mg, 66%); ¹H NMR (400 MHz, CDCl₃) δ: 8.29 (s, 1H), 6.93 (s, 2H), 4.53 (sep, *J* = 6.9 Hz, 1H), 3.69 (sep, *J* = 6.8 Hz, 1H), 2.69 (s, 6H), 2.30 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 155.7, 141.0, 138.3, 136.6, 131.4, 48.2, 47.7, 23.7, 22.9, 20.9, 19.7.



(*E*)-*N*'-(*p*-Methylphenyl)sulfonyl)-*N*-ethyl-*N*'-phenylformimidamide (3p)²⁶

White solid (139 mg, 46%); ¹H NMR (400 MHz, CDCl₃) δ: 8.48 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.50–7.43 (m, 2H), 7.40–7.37 (m, 1H), 7.34–7.30 (m, 2H), 7.26–7.18 (m, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.1, 142.7, 141.9, 139.1, 129.9, 129.4, 127.7, 126.6, 123.6, 44.1, 21.5, 12.4.

***N,N*-Bis(hydroxymethyl)-4methylbenzenesulfonamide (4)²⁷**

Colorless oil (143 mg, 46%); ¹H NMR (400 MHz, CDCl₃) δ: 7.72 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.12 (s, 2H), 3.88 (t, *J* = 4.9 Hz, 4H), 3.28 (t, *J* = 4.8 Hz, 4H), 2.45 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 143.8, 135.2, 129.9, 127.3, 62.3, 53.0, 21.5.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Institute for Advanced Studies in Basic Sciences is thanked for supporting this work. The authors also wish to thank Mr Haruhiko Fukaya, Tokyo University of Pharmacy and Life Sciences, for his help carrying out the HRMS measurements.

References

- 1 M. P. Coles, Application of neutral amidines and guanidines in coordination chemistry, *Dalton Trans.*, 2006, 985–1001.
- 2 J. Barker and M. Kilner, The coordination chemistry of the amidine ligand, *Coord. Chem. Rev.*, 1994, **133**, 219–300.
- 3 J. V. Greenhill and P. Lue, Amidines and guanidines in medicinal chemistry, *Prog. Med. Chem.*, 1993, **30**, 203–326.
- 4 P. Sienkiewicz, K. Bielawski, A. Bielawska and J. Palka, Inhibition of collagen and DNA biosynthesis by a novel amidine analogue of chlorambucil is accompanied by deregulation of β1-integrin and IGF-I receptor signaling in MDA-MB 231 cells, *Environ. Toxicol. Pharmacol.*, 2005, **20**, 118–124.
- 5 M. Wang, Y. Liu, L. Chang, C. Wang, Y. Zhao, X. Zhao, K. Qian, X. Nan, L. Yang, X. Yang, H. Hung, J. Yang, D. Kuo, M. Goto, S. Morris-Natschke, S. Pan, C. Teng, S. Kuo, T. Wu, Y. Wu and K. Lee, Design, Synthesis, Mechanisms of Action, and Toxicity of Novel 20(*S*)-Sulfonylamidine Derivatives of Camptothecin as Potent Antitumor Agents, *J. Med. Chem.*, 2014, **57**, 6008–6018.
- 6 T. Beryozkina, V. Bakulev, L. Dianova, V. Berseneva, P. Slepukhin, J. Leban, P. Kalaba, N. Y. Aher, M. Ilic, H. H. Sitte and G. Lubec, Design and Synthesis of *N*-Sulfonylamidines of Modafinil Acid, *Synthesis*, 2016, **48**, 1046–1054.
- 7 Z. L. Song, H. L. Chen, Y. H. Wang, M. Goto, W. J. Gao, P. L. Cheng, S. L. Cheng, Morris-Natschke, Y. Q. Liu, G. X. Zhu, M. J. Wang and K. H. Lee, Design and synthesis of novel PEG-conjugated 20(*S*)-camptothecin sulfonylamidine derivatives with potent in vitro antitumor activity via Cu-catalyzed three-component reaction, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2690–2693.
- 8 M. Y. Lee, M. H. Kim, J. Kim, S. H. Kim, B. T. Kim, I. H. Jeong, S. Chang, S. H. Kim and S.-Y. Chang, Synthesis and SAR of sulfonyl- and phosphoryl amidine compounds as anti-resorptive agents, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 541–545.
- 9 T. D. Suja, K. V. L. Divya, L. V. Naik, A. R. Kumar and A. Kamal, Copper-catalyzed three-component synthesis of aminonaphthoquinone-sulfonylamidine conjugates and in vitro evaluation of their antiproliferative activity, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 2072–2076.
- 10 L.-Y. Xie, T.-G. Fang, J.-X. Tan, B. Zhang, Z. Cao, L.-H. Yang and W.-M. He, Visible-light-induced deoxygenative C2-sulfonylation of quinoline N-oxides with sulfinic acids, *Green Chem.*, 2019, **21**, 3858–3863.
- 11 S. Peng, Y.-X. Song, J.-Y. He, S.-S. Tang, J.-X. Tan, Z. Cao, Y.-W. Lin and W.-M. He, TsCl-promoted sulfonylation of quinoline N-oxides with sodium sulfinates in water, *Chin. Chem. Lett.*, 2019, **30**, 2287–2290.
- 12 L.-Y. Xie, S. Peng, F. Liu, G.-R. Chen, W. Xia, X. Yu, W.-F. Li, Z. Cao and W.-M. He, Metal-free deoxygenative sulfonylation of quinoline N-oxides with sodium sulfinates via a dual radical coupling process, *Org. Chem. Front.*, 2018, **5**, 2604–2609.
- 13 S. Chen, Y. Xu and X. Wan, Direct Condensation of Sulfonamide and Formamide: NaI-Catalyzed Synthesis of *N*-Sulfonyl Formamidines Using TBHP as Oxidant, *Org. Lett.*, 2011, **13**, 6152–6155.
- 14 J. Chen, W. Long, S. Fang, Y. Yang and X. Wan, Interception of amide ylides with sulfonamides: synthesis of (*E*)-*N*-sulfonyl amidines catalyzed by Zn(OTf)₂, *Chem. Commun.*, 2017, **53**, 13256–13259.
- 15 I. Bae, H. Han and S. Chang, Highly Efficient One-Pot Synthesis of *N*-Sulfonylamidines by Cu-Catalyzed Three-Component Coupling of Sulfonyl Azide, Alkyne, and Amine, *J. Am. Chem. Soc.*, 2005, **127**, 2038–2039.
- 16 S. Chow and L. R. Odell, Synthesis of *N*-Sulfonyl Amidines and Acyl Sulfonyl Ureas from Sulfonyl Azides, Carbon Monoxide, and Amides, *J. Org. Chem.*, 2017, **82**, 2515–2522.
- 17 W.-Z. Bi, W.-J. Zhang, Z.-J. Li, X.-Y. Xia, X.-L. Chen, L.-B. Qu and Y.-F. Zhao, Air-induced one-pot synthesis of *N*-sulfonylformamidines from sulfonyl chlorides, NaN₃ and tertiary/secondary amines, *Eur. J. Org. Chem.*, 2019, **2019**, 6071–6076.
- 18 X. Xu, Z. Ge, D. Cheng, C. Ma, L. Ma, C. Lu, Q. Zhang, N. Yao and X. Li, CuCl/CCl₄-Promoted Convenient Synthesis of Sulfonyl Amidines from Tertiary Amines and Sulfonyl Azides, *Org. Lett.*, 2010, **12**, 897–899.
- 19 S. Wang, Z. Wang and X. Zheng, Facile synthesis of sulfonylamidines via carbon–nitrogen bond formation mediated by FeCl₃, *Chem. Commun.*, 2009, 7372–7374.
- 20 X. Xu, X. Li, L. Ma, N. Ye and B. Weng, An Unexpected Diethyl Azodicarboxylate-Promoted Dehydrogenation of Tertiaryamine and Tandem Reaction with Sulfonyl Azide, *J. Am. Chem. Soc.*, 2008, **130**, 14048–14049.



- 21 J. Gui, H. Xie, H. Jian and W. Zeng, Visible-Light-Mediated Sulfonylimination of Tertiary Amines with Sulfonylazides Involving $C_{sp^3}-C_{sp^3}$ Bond Cleavage, *Org. Lett.*, 2019, **21**, 2804–2807.
- 22 R. Ding, H. Chen, Y.-L. Xu, H.-T. Tang, Y.-Y. Chen and Y.-M. Pan, Photoinduced Cascade Reaction of Tertiary Amines with Sulfonyl Azides: Synthesis of Amidine Derivatives, *Adv. Synth. Catal.*, 2019, **361**, 3656–3660.
- 23 L. Zhang, J.-H. Su, S. Wang, C. Wan, Z. Zha, J. Du and Z. Wang, Direct electrochemical imidation of aliphatic amines via anodic oxidation, *Chem. Commun.*, 2011, **47**, 5488–5490.
- 24 B. Kaboudin, A. Zangoeei, F. Kazemi and T. Yokomatsu, Catalyst-free Petasis-type reaction: three-component decarboxylative coupling of boronic acids with proline and salicylaldehyde for the synthesis of alkylaminophenols, *Tetrahedron Lett.*, 2018, **59**, 1046–1049.
- 25 B. Kaboudin, L. Karami, J.-Y. Kato, H. Aoyama and T. Yokomatsu, A catalyst-free, three-component decarboxylative coupling of amino acids with aldehydes and *H*-dialkylphosphites for the synthesis of α -aminophosphonates, *Tetrahedron Lett.*, 2013, **54**, 4872–4875.
- 26 A. Rouzi, R. Hudabaierdi and A. Wusiman, Synthesis of *N*-sulfonylformamidines by *tert*-butyl hydroperoxide-promoted, metal-free, direct oxidative dehydrogenation of aliphatic amines, *Tetrahedron*, 2018, **74**, 2475–2481.
- 27 M. Arisawa, C. Kato, H. Kaneko, A. Nishida and M. Nakagawa, Concise synthesis of azacycloundecenes using ring-closing metathesis (RCM), *J. Chem. Soc., Perkin Trans. 1*, 2000, 1873–1876.

