A Novel and Efficient Regiospecific Preparation of Arenesulfonamide Derivatives of 3,5-Diamino-1,2,4-triazole

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Abstract: A new simple and efficient procedure was designed for the regiospecific preparation of arenesulfonamide derivatives of 3,5-diamino-1,2,4-triazole **1** which are precursors of *N*-([1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)arenesulfonamides **2**, an important family of herbicidal and antibacterial agents. The key feature of this procedure is the preparation of a wide range of compounds **1** on a large scale, in pure form and high yield without the need for any workup or the use of the highly hazardous hydrazine. This was made possible by a novel tandem reaction promoted by sulfuryl chloride to effect the formation of the triazole ring.

Key words: triazole ring formation, heterocycles, cyclizations, tandem reactions, herbicidal agents

N-(5-Amino-1*H*-[1,2,4]triazol-3-yl)arenesulfonamides **1** are key intermediates in the synthesis of *N*-([1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)arenesulfonamides **2** (Figure 1), a class of compounds displaying important herbicidal and antibacterial activities.[2] As part of our ongoing medicinal chemistry project, we intended to prepare chemical libraries of compounds **2** in array format for lead optimization. Hence we needed a straightforward and simple approach to prepare large quantities of building blocks **1**. The procedures described previously in the literature[3,4] both involve a two-step formation of the triazole ring from commercially or readily available arenesulfonamides **3**. However, both methods exhibit several disadvantages including the use of reflux[3] or high temperature[4] conditions, moderate and inconsistent yields[3,4] as well as the use of two highly hazardous chemicals, hydrazine[3] or carbon disulfide.[4] We reasoned that the first procedure[3] involving a two-step construction of the heterocyclic ring starting from **3** and dimethyl cyanodithioiminocarbonate (**4**) was amenable to optimisation in order to avoid the aforementioned drawbacks. In the original publication, two different methods were described for the first step yielding the intermediate methyl *N*-(arylsulfonyl)-*N'*-cyanoimidothiocarbamates **5**, but both required reflux conditions and yields were inconsistent and often quite low. The second step involved hydrazine as a reagent, and was thus unsatisfactory on safety grounds.

The initial objective of our research programme was to simplify the experimental procedure and increase the yields in the first step as well as finding alternative and safer reaction conditions for the second step. In this paper, we wish to report both improvements in the preparation of the building blocks **1**, as well as the use of sulfuryl chloride in a new tandem reaction leading to the construction of the triazole ring.

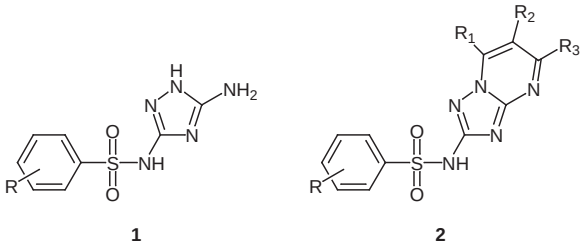

Figure 1 Chemical structures of arenesulfonamides **1** and **2**

To perform the coupling of **3** and **4**, we were looking for a simplified procedure which avoids reflux conditions and affords compounds **5** in higher and more consistent yields. Presumably reflux conditions were desirable in order to address solubility problems. We decided to use DMF as a solvent for the coupling in order to circumvent these problems. This choice consequently allowed us to work with highly concentrated reaction media. We used potassium carbonate as a base due to its water solubility which, coupled with the water miscibility of DMF simplified the final product isolation procedure. As a matter of fact, operating with concentrations as high as 3 molar, we were able to precipitate the pure products **5** in high yields (Table 1) by simply adding aqueous 2 M hydrochloric acid to the reaction mixture.

It is noteworthy that the new procedure resulted in a dramatic increase in isolated yields of products compared with the previously published results, as shown below. The high concentration of the reaction medium and the simplicity of the purification process certainly accounts for the substantial improvement in chemical yields observed.

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Table 1 Compounds **5** Synthesized

Compound	R	Yield[a] (%)
5a	H	82 (45)
5b	4-Me	83 (55)
5c	4-Cl	92
5d	2-Cl	99 (69)
5e	3-Cl	95
5f	4-Br	88
5g	2-naphthyl[b]	87
5h	2,4,6-Pr-*i*	97 (40)
5i	2-CO_2Me	77
5j	4-OMe	88

[a] Yields reported in the literature[3] are given in parenthesis.
[b] 2-Naphthylsulfonamide (**3g**) was used in place of benzenesulfonamide (**3a**, R = H).

Following the previously described procedure, the second step required the use of either anhydrous hydrazine or hydrazine monohydrate, which are both highly toxic and dangerous chemicals. Thus we clearly needed to find a different approach in order to comply with health and safety regulations. The most evident choice appeared to be the utilization of *tert*-butyl carbazate, a protected hydrazine derivative usually used as its equivalent in synthesis, or as a way of introducing the Boc protecting group.

We initially envisaged carrying out the coupling of compounds **5** with *tert*-butyl carbazate followed by addition of trifluoroacetic acid (TFA) to deprotect the expected intermediate adduct **6** in situ (Scheme 1) and effect the cyclization leading to the formation of the triazole ring. Unfortunately, our attempts using this strategy were unsatisfactory. Reactions with both compounds **5a** and **5b** using TFA for deprotection and subsequent cyclization yielded a mixture of compounds **1a** and **1b** respectively, together with 3-amino-5-methylthio-1,2,4-triazole (**7**) (Figure 2) as a major byproduct (over 50% in both cases). The coupling typically required heating to 60 °C for good reaction rates. Different solvents (dichloromethane, acetonitrile, 1,4-dioxane) and conditions (adding TFA in the first place or after the intermediate **6** has formed, isolating **6** and carrying out the second step at room temperature using diluted hydrochloric acid instead of TFA) were tried but none gave satisfactory results.

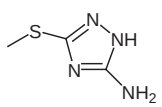

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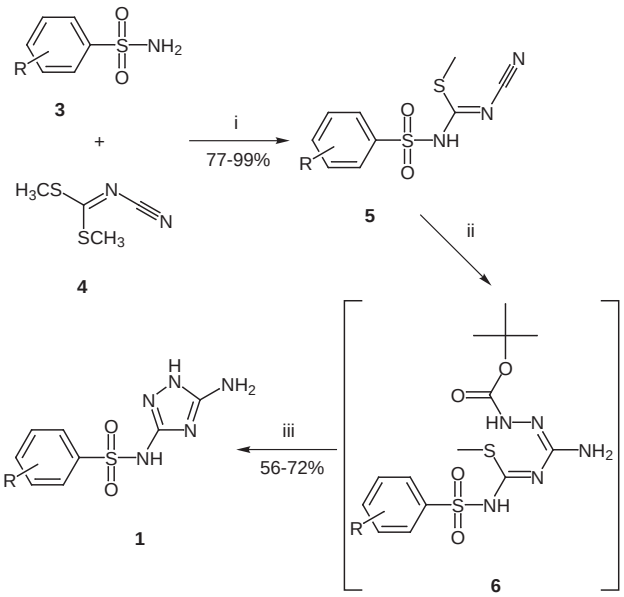
Figure 2 Chemical structure of the byproduct 1,2,4-triazole **7**



Scheme 1 Synthesis of triazoles **1** *Reagents and conditions*: i) K_2CO_3/DMF, r.t., then 2 N aq HCl; ii) *t*-BuNHNH$_2$/MeCN, 60 °C; iii) a. SO_2Cl_2/CH_2Cl_2, r.t., b. EtOH–H_2O, Δ

At this juncture we were prompted to think about an alternative method for the smooth and selective tandem deprotection-cyclization protocol for accessing our target compounds **1**. The previous experiments revealed that under the reaction conditions used, elimination of the arenesulfonamide moiety was surprisingly highly competitive with the elimination of methanethiol during the addition-elimination process leading to the formation of the triazole ring. The challenge was for us to find conditions favoring the elimination of the sulfide moiety, possibly by increasing its tendency to behave as a good leaving group. At this point our attention turned to sulfuryl chloride.

It is known in the literature that sulfuryl chloride is a powerful chlorinating agent capable of generating chlorine in situ. Besides this, sulfuryl chloride is also known to catalyze the deprotection of *tert*-butyl esters. Although sulfuryl chloride is well documented as a carbon chlorinating agent, its use as a sulfur chlorinating agent is rare.[5] We reasoned that chlorine generated in situ from the sulfuryl chloride-mediated deprotection of the *tert*-butoxycarbonyl (Boc) group might lead to chlorination of the methyl sulfide moiety to generate a methylchlorosulfonium cation and subsequent elimination of methylsulfenyl chloride. Gratifyingly, we found that treatment of the isolated crude intermediate **6** in the presence of sulfuryl chloride in dichloromethane at room temperature mainly gave the expected arenesulfonamide derivative of triazole **1**, which simply precipitated out of solution. In most cases, the amount of byproduct **7** was less than 10%. Subsequently we also found that refluxing a suspension of the crude solid for a few minutes in a 1:1 mixture of ethanol and water allowed us, after filtration, to obtain compounds **1** in pure form without dramatically affecting the yield of the two-step procedure (Table 2).

Table 2 Preparation of **1**

Compound	R	Yield[a] (%)
1a	H	72 (70)
1b	4-Me	56 (89)
1c	4-Cl	67
1d	2-Cl	60 (77)
1e	3-Cl	63
1f	4-Br	62
1g	2-naphthyl[b]	68
1h	2,4,6-*i*-Pr	64 (84)

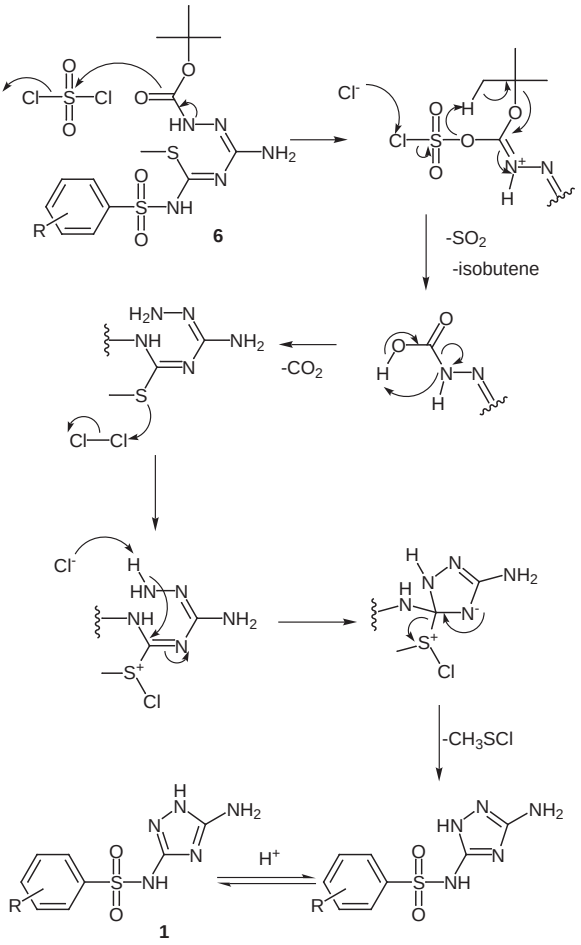
[a] Yield over two steps. Yields reported in the literature[3] are given in parenthesis.
[b] Methyl *N'*-cyano-*N*-(2-naphthylsulfonyl)imidothiocarbamate (**5g**) was used in place of methyl *N'*-cyano-*N*-(phenylsulfonyl)imidothiocarbamate (**5a**, R = H).

The only limitation observed with this method was in the case of compounds **5i** and **5j**. TLC monitoring of the reaction in these cases revealed the formation of a number of byproducts, which probably resulted from sensitivity of the ester[6] and ether[7] moieties to sulfuryl chloride.

In order to account for the modified reactivity of compounds **6** under the conditions described above, we propose the mechanism depicted in Scheme 2. In this mechanism, the reaction is initiated by the sulfuryl chloride-mediated deprotection of the Boc group in which chlorine is generated. Subsequent chlorination of the methyl sulfide moiety to give the corresponding chlorosulfonium cation is accompanied by concomitant cyclization. Since sulfuryl chloride is known to generate Cl_2 in situ, it is reasonable to envisage an alternative mechanism involving initial chlorination followed by Boc deprotection.

A summary of the overall yields obtained for transformation **3** → **1** in comparison with those from previously described procedures is presented in Table 3. Whereas all results are at least as good as those previously reported, a dramatic increase in the yields was observed in some cases. This clearly demonstrates that avoiding the use of hydrazine or carbon disulfide does not adversely affect the efficiency of the preparation of the title compounds.

In conclusion, we have described an efficient and high yielding route to the preparation of *N*-(5-amino-1*H*-[1,2,4]triazol-3-yl)arenesulfonamides **1** of high purity from commercially available arenesulfonamides **3**. This new procedure avoids using highly hazardous hydrazine and also excludes any purification techniques other than filtration. In this respect, it is perfectly suited for large scale synthesis as demonstrated here on 5 g batches. The series of compounds **2** prepared as described in this paper will be used as scaffolds for the generation of chemical libraries of *N*-([1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)arenesulfonamides **2**. In addition, we have presented an interesting utilization of sulfuryl chloride, a powerful and versatile inorganic reagent for organic synthesis, in a novel tandem reaction for which a plausible mechanism has been proposed.



Scheme 2 Proposed mechanism for the sulfuryl chloride initiated tandem reaction

Table 3 Comparison of the Overall Yields for the Transformation **3** → **1**

Preparation	R	Yield[a] (%)
3a → **1a**	H	59 (32,[3] 35[4])
3b → **1b**	4-Me	46 (49,[3] 41[4])
3c → **1c**	4-Cl	62 (35[4])
3d → **1d**	2-Cl	59 (53[3])
3h → **1h**	2,4,6-Pr-*i*	62 (34[3])

[a] Overall yield. Literature yields are given in parenthesis.

All materials were purchased from commercial suppliers and used without further purification. Dimethyl cyanodithioiminocarbonate was purchased from Lancaster (99% purity). TLC was performed on aluminum backed silica gel 60 F_{254} plates and visualized by UV light. Melting points were measured using a Reichert–Jung Thermovar hot-stage microscope and are uncorrected. Microanalyses

were determined using a Fisons EA 1108 CHNS-O instrument. Mass spectra (EI) were recorded on a VG Micromass 16F spectrometer. All ^{1}H NMR spectra were recorded on a Varian Gemini (300 MHz) or a Varian Unity Spectrometer (400 MHz), using the residual proton signal of the deuterated solvent as an internal reference: for $CDCl_3$ (δ = 7.26), acetone-d_6 (δ = 2.05), and DMSO-d_6 (δ = 2.50). All ^{13}C NMR spectra were recorded on the same instruments at 75 MHz or 100 MHz, using the ^{13}C signal of the deuterated solvent as an internal reference: for $CDCl_3$ (δ = 77.0, central signal), acetone-d_6 (δ = 29.8, central signal, and δ = 205.7), and DMSO-d_6 (δ = 39.6, central signal). For the ^{1}H NMR spectral data, coupling constants (J) are reported in Hz. Carbon multiplicities were assigned by DEPT experiments. Some quaternary carbon atoms have very slow relaxation times, in which case they do not appear in the assignment.

Methyl *N*-(Arylsulfonyl)-*N'*-cyanoimidothiocarbamates 5a–j; General Procedure

A mixture of arenesulfonamide **3a–j** (6.4 mmol), an equimolar amount of both dimethyl *N*-cyanodithioiminocarbonate and finely ground anhyd K_2CO_3 in DMF (10 mL) were stirred at r.t. for 15 h. Then an aq solution of 2 N HCl (150 mL) was added to the reaction mixture and stirred for an additional 8 h. The white precipitate formed was collected by filtration and washed successively with an aq solution of 2 N HCl and a small amount of ether. Further drying under vacuum afforded the imidothiocarbamate **5a–j**. The yields are listed in Table 1.

Methyl *N'*-Cyano-*N*-(phenylsulfonyl)imidothiocarbamate (5a)

Scale: 31.8 mmol; white solid; mp 132–134 °C (Lit.[3] mp 122 °C, dec.); R_f 0.18 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.76 (s, 3 H, SCH_3), 7.68 (m, 2 H_{arom}, H_{meta}), 7.77 (m, 1 H_{arom}, H_{para}), 8.03 (m, 2 H_{arom}, H_{ortho}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 14.9 (CH_3), 128.6 (2 × CH), 129.4 (2 × CH), 134.6 (CH), 170.9 (C).

MS (EI): m/z (%) = 255 (M^+, 1), 208 ($M^+ - SCH_3$, 10), 141 ($PhSO_2^+$, 42), 77 (Ph^+, 100).

Anal. Calcd for $C_9H_9N_3O_2S_2$: C, 42.34; H, 3.55; N, 16.46; S, 25.11. Found: C, 42.24; H, 3.30; N, 16.39; S, 25.02.

Methyl *N'*-Cyano-*N*-[(4-methylphenyl)sulfonyl]imidothio-carbamate (5b)

Scale: 29.2 mmol; white solid; mp 133–134 °C (Lit.[3] mp 137.5–139 °C); R_f 0.19 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.46 (s, 3 H, CH_3), 2.75 (s, 3 H, SCH_3), 7.49 (d, 2 H_{arom}, J = 8.4 Hz, H_{meta}), 7.91 (d, 2 H_{arom}, J = 8.4 Hz, H_{ortho}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 14.8 (CH_3), 20.9 (CH_3), 111.7 (C), 128.8 (2 × CH), 129.9 (2 × CH), 135.8 (C), 145.9 (C), 170.9 (C).

MS (EI): m/z (%) = 269 (M^+, 1), 222 ($M^+ - SCH_3$, 6), 155 ($C_6H_4CH_3SO_2^+$, 59), 91 ($C_6H_4CH_3^+$, 100).

Anal. Calcd for $C_{10}H_{11}N_3O_2S_2$: C, 44.59; H, 4.12; N, 15.60; S, 23.81. Found: C, 44.96; H, 3.89; N, 15.93; S, 24.20.

Methyl *N*-[(4-Chlorophenyl)sulfonyl]-*N'*-cyanoimidothio-carbamate (5c)

Scale: 20.9 mmol; white solid; mp 133–134 °C; R_f 0.15 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.77 (s, 3 H, SCH_3), 7.72 (d, 2 H_{arom}, J = 8.8 Hz, H_{meta}), 8.03 (d, 2 H_{arom}, J = 8.8 Hz, H_{ortho}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 15.7 (CH_3), 112.2 (C), 130.5 (2 × CH), 131.4 (2 × CH), 138.5 (C), 141.3 (C), 171.9 (C).

MS (EI): m/z (%) = 289 (M^+, 1), 242 ($M^+ - SCH_3$, 9), 175 ($C_6H_4ClSO_2^+$, 68), 111 ($C_6H_4Cl^+$, 100).

Anal. Calcd for $C_9H_8ClN_3O_2S_2$: C, 37.31; H, 2.78; N, 14.50; S, 22.13. Found: C, 37.18; H, 2.42; N, 14.61; S, 22.31.

Methyl *N*-[(2-Chlorophenyl)sulfonyl]-*N'*-cyanoimidothio-carbamate (5d)

Scale: 26.1 mmol; white solid; mp 132–133 °C (Lit.[3] mp 126.5 °C, dec.); R_f 0.14 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (300 MHz, acetone-d_6): δ = 2.78 (s, 3 H, SCH_3), 7.61–7.80 (m, 3 H_{arom}, 2 H_{meta} and 1 H_{para}), 8.19 (dd, 1 H_{arom}, J = 8.0 Hz, J = 1.4 Hz, H_{ortho}).

^{13}C NMR (75 MHz, acetone): δ = 16.3 (CH_3), 112.0 (C), 129.2 (CH), 133.2 (C), 133.5 (CH), 134.0 (CH), 137.1 (CH), 137.9 (C), 171.7 (C).

LRMS (EI): m/z (%) = 289 (M^+, 3), 242 ($M^+ - SCH_3$, 12), 207 ($M^+ - SCH_3 - Cl$, 10), 175 ($C_6H_4ClSO_2^+$, 66), 111 ($C_6H_4Cl^+$, 100).

Anal. Calcd for $C_9H_8ClN_3O_2S_2$: C, 37.31; H, 2.78; N, 14.50; S, 22.13. Found C, 37.21; H, 2.40; N, 14.55; S, 22.51.

Methyl *N*-[(3-Chlorophenyl)sulfonyl]-*N'*-cyanoimidothio-carbamate (5e)

Scale: 26.1 mmol; white solid; mp 129–130 °C; R_f 0.11 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (300 MHz, acetone-d_6): δ = 2.77 (s, 3 H, CH_3), 7.71 (m, 1 H_{arom}, H_{meta}), 7.80 (m, 1 H_{arom}, H_{para}), 7.98 (m, 1 H_{arom}, H_{ortho}), 8.00 (d, 1 H_{arom}, J = 1.5, H_{ortho}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 15.2 (CH_3), 111.6 (C), 127.5 (CH), 128.5 (CH), 131.6 (CH), 134.8 (CH), 135.0 (C), 141.5 (C), 171.5 (C).

Anal. Calcd for $C_9H_8ClN_3O_2S_2$: C, 37.31; H, 2.78; N, 14.50; S, 22.13. Found C, 37.62; H, 2.36; N, 14.74; S, 22.50.

Methyl *N*-[(4-Bromophenyl)sulfonyl]-*N'*-cyanoimidothio-carbamate (5f)

Scale: 21.2 mmol; white solid; mp 132–133 °C; R_f 0.11 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.77 (s, 3 H, CH_3), 7.88 (d, 2 H_{arom}, J = 8.8 Hz, H_{meta}), 7.96 (d, 2 H_{arom}, J = 8.8 Hz, H_{ortho}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 15.9 (CH_3), 112.3 (C), 130.1 (C), 131.6 (CH), 133.7 (CH), 139.2 (C), 171.9 (C).

Methyl *N'*-Cyano-*N*-(2-naphthylsulfonyl)imidothiocarbamate (5g)

Scale: 24.1 mmol; white solid; mp 138–140 °C; R_f 0.14 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.77 (s, 3 H, CH_3), 7.75 (td, 1 H, J = 8.1, 1.6 Hz), 7.78 (td, 1 H, J = 8.1, 1.6 Hz), 8.02 (dd, 1 H, J = 8.8, 2.0 Hz), 8.08 (d, 1 H, J = 8.1 Hz), 8.18 (d, 1 H, J = 8.8 Hz), 8.20 (d, 1 H, J = 8.1 Hz), 8.69 (d, 1 H, J = 2.0 Hz).

^{13}C NMR (100 MHz, acetone-d_6): δ = 16.0 (CH_3), 112.5 (C), 124.1 (CH), 129.2 (CH), 129.3 (CH), 130.7 (CH), 130.9 (CH), 131.0 (CH), 131.8 (CH), 133.2 (C), 136.8 (C), 136.9(C), 171.9 (C).

Methyl *N'*-Cyano-*N*-[(2,4,6-triisopropylphenyl)sulfonyl]imido-thiocarbamate (5h)

Scale: 17.6 mmol; white solid; mp 237–238 °C (dec.) (Lit.[3] mp 165–165.5 °C); R_f 0.18 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.19 (d, 12 H, J = 6.6 Hz, $CHCH_3$), 1.23 (d, 6 H, J = 6.6 Hz, $CHCH_3$), 2.33 (s, 3 H, SCH_3), 2.90 (septet, 1 H, J = 6.6, $CHCH_3$), 3.40 (br s, 1 H, NH), 4.61 (septet, 2 H, J = 6.6 Hz, $CHCH_3$), 7.14 (s, 2 H_{arom}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 15.1 (CH_3), 23.4 (2 × CH_3), 24.4 (4 × CH_3), 29.1 (2 × CH), 34.1 (CH), 122.8 (2 × CH), 138.0 (C), 149.7 (C), 150.6 (C).

Methyl 2-({[(Cyanoimino)(methylsulfanyl)methyl]amino}sulfonyl)benzoate (5i)

Scale: 23.2 mmol; white solid; mp 133 °C; R_f 0.29 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz,acetone-d_6): δ = 2.75 (s, 3 H, SCH_3), 3.98 (s, 3 H, CO_2CH_3), 7.84–7.92 (m, 3 H_{arom}, 2 H_{meta} and 1 H_{para}), 8.23 (d, 1 H_{arom}, J = 7.2 Hz, H_{ortho}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 14.6 (CH_3), 53.2 (CH_3), 111.1 (C), 130.7 (CH), 131.7 (2 × CH), 132.3 (C), 134.8 (CH), 136.6 (C), 167.2 (C), 170.6 (C).

LRMS (EI): m/z (%) = 314 (M^+, 0.1), 199 [$C_6H_4(CO_2CH_3)SO_2^+$, 100], 135 ($C_6H_4CO_2CH_3^+$, 41), 120 ($C_6H_4CO_2^+$, 7), 77 (Ph^+, 43).

Anal. Calcd for $C_{11}H_{11}N_3O_4S_2$: C, 42.16; H, 3.54; N, 13.41; S, 20.46. Found: C, 42.10; H, 3.29; N, 13.43; S, 20.44.

Methyl *N'*-Cyano-*N*-[(4-methoxyphenyl)sulfonyl]imidothiocarbamate (5j)

Scale: 26.7 mmol; white solid; mp 135–136 °C; R_f 0.18 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (300 MHz, acetone-d_6): δ = 2.75 (s, 3 H, SCH_3), 3.94 (s, 3 H, OCH_3), 7.16 (dt, 2 H_{arom}, J = 9.0, 2.5 Hz, H_{meta}), 7.96 (dt, 2 H_{arom}, J = 9.0, 2.5 Hz, H_{ortho}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 16.1 (CH_3), 24.9 (C), 57.0 (CH_3), 113.5 (C), 115.8 (2 × CH), 131.2 (C), 132.6 (2 × CH), 166.0 (C).

LRMS (EI): m/z (%) = 285 (M^+, 7), 238 ($M^+ - SCH_3$, 2), 171 [$C_6H_4(OCH_3)SO_2^+$, 100], 107 ($C_6H_4OCH_3^+$, 67), 77 (Ph^+, 52).

Anal. Calcd for $C_{10}H_{11}N_3O_3S_2$: C, 42.09; H, 3.89; N, 14.73; S, 22.47. Found: C, 41.98; H, 3.74; N, 14.82; S, 22.59.

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)arenesulfonamides 1a–h; General Procedure**

A mixture of **5a**–**j** (15.0 mmol), and *tert*-butyl carbazate (1.98 g, 15.0 mmol) in MeCN (50 mL) was stirred and heated to 60 °C for 16 h. Then the mixture was evaporated to dryness to yield the crude intermediate **6a**–**j** as a white or pale yellow foam. SO_2Cl_2 (1.45 mL, 18.0 mmol) was added to a stirred solution of this crude intermediate in CH_2Cl_2 (250 mL). The pale yellow precipitate formed after overnight stirring at r.t. was collected by filtration and washed with CH_2Cl_2. The solid residue was suspended in 50% aq EtOH (100 mL) and the mixture was refluxed for 15 min, then allowed to cool to r.t. The solid was collected by filtration and washed successively with H_2O and a small amount of Et_2O. Further drying under vacuum afforded **1a**–**h**. The yields over 2 steps are listed in Table 2.

Intermediate 6a

White foam; R_f 0.75 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*-C_4H_9), 2.31 (s, 3 H, SCH_3), 7.23 (br s, 1 H, NH), 7.44 (m, 2 H_{arom}, H_{meta}), 7.50 (m, 1 H_{arom}, H_{para}), 7.75 (br s, 1 H, NH), 7.92 (m, 2 H_{arom}, H_{ortho}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (CH_3), 28.1 (3 × CH_3), 82.8 (C), 127.1 (2 × CH), 128.5 (2 × CH), 131.9 (CH), 141.9 (C), 155.2 (C), 158.5 (C), 175.4 (C).

LRMS (FAB+): m/z = 410 (MNa^+), 388 (MH^+), 332 (M^+ – *t*-Bu).

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)benzenesulfonamide (1a)**

White solid; mp 293–294 °C (dec.) (Lit.[4] mp 289 °C); R_f 0.18 ($CHCl_3$–EtOH, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.82 (br s, 2 H, NH_2), 7.46–7.53 (m, 3 H_{arom}, 2 H_{meta} and 1 H_{para}), 7.78 (dd, 2 H_{arom}, J = 8.0, 1.6 Hz, H_{ortho}), 11.40–11.90 (br s, 2 H, 2 × NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.9 (C), 117.7 (C), 125.7 (2 × CH), 128.7 (2 × CH), 131.5 (CH), 148.7 (C).

HRMS (EI): m/z calcd for $C_8H_9N_5O_2S$ (M^+) 239.0480, found 230.0477; 175 ($M^+ - SO_2$, 7), 141 ($M^+ - C_2H_4N_5$, 7), 98 ($C_2H_4N_5^+$, 100), 77 (Ph^+, 69).

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)-4-methylbenzenesulfonamide (1b)**

White solid; mp 312 °C (Lit.[3] mp 314–315 °C (Lit.[4] mp 306 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (s, 3 H, CH_3), 5.83 (br s, 2 H, NH_2), 7.30 (d, 2 H_{arom}, J = 7.9 Hz, H_{meta}), 7.69 (d, 2 H_{arom}, J = 7.9 Hz, H_{ortho}), 11.40 (br s, 1 H, NH), 11.68 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.8 (CH_3), 125.7 (2 × CH), 129.1 (2 × CH), 141.3 (C).

LRMS (EI): m/z (%) = 253 (M^+, 36), 189 ($M^+ - SO_2$, 12), 155 ($M^+ - C_2H_4N_5$, 11), 98 ($C_2H_4N_5^+$, 83), 91 ($C_6H_4CH_3^+$, 100).

Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 42.7; H, 4.4; N, 27.65; S, 12.7. Found: C, 42.3; H, 4.1; N, 27.5; S, 12.0.

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)-4-chlorobenzenesulfonamide (1c)**

White solid; mp 311–312 °C (dec.) (Lit.[4] mp 299 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.87 (br s, 2 H, NH_2), 7.57 (d, 2 H_{arom}, J = 8.8, H_{meta}), 7.80 (d, 2 H_{arom}, J = 8.8, H_{ortho}), 11.57 (br s, 1 H, NH), 11.78 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 127.5 (C), 128.8 (4 × CH), 136.0 (C).

LRMS (EI): m/z (%) = 273 (M^+, 12), 111 ($C_6H_4Cl^+$, 36), 98 ($C_2H_4N_5^+$, 84).

Anal. Calcd for $C_8H_8ClN_5O_2S$: C, 35.1; H, 3.0; N, 25.6; S, 11.7. Found: C, 35.2; H, 2.8; N, 25.8; S, 11.3.

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)-2-chlorobenzenesulfonamide (1d)**

White solid, mp 315–316 °C (Lit.[3] mp 307–309 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.85 (br s, 2 H, NH_2), 7.44 (td, 1 H_{arom}, J = 7.6, 1.6 Hz, H_{para}), 7.51 (td, 1 H_{arom}, J = 7.6, 1.6 Hz, H_{meta}), 7.55 (dd, 1 H_{arom}, J = 7.6, 1.6 Hz, H_{meta}), 8.02 (dd, 1 H_{arom}, J = 7.6, 1.6 Hz, H_{ortho}), 11.49 (br s, 1 H, NH), 11.92 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 127.8 (CH), 129.9 (CH), 131.3 (C), 132.1 (CH), 133.3 (CH), 142.1 (C), 149.3 (C), 150.9 (C).

LRMS (EI): m/z (%) = 273 (M^+, 29), 238 (M^+ – Cl, 4), 209 ($M^+ - SO_2$, 3), 174 ($M^+ - C_2H_4N_5$, 8), 111 ($C_6H_4Cl^+$, 32), 98 ($C_2H_4N_5^+$, 100).

Anal. Calcd for $C_8H_8ClN_5O_2S$: C, 35.1; H, 3.0; N, 25.6; S, 11.7. Found: C, 35.5; H, 2.7; N, 25.2; S, 11.4.

***N*-(5-Amino-1*H*-[1,2,4]triazol-3-yl)-3-chlorobenzenesulfonamide (1e)**

White solid; mp 306–308 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.89 (br s, 2 H, NH_2), 7.51–7.62 (m, 2 H_{arom}, H_{meta} and H_{para}), 7.74 (dt, 1 H_{arom}, J = 7.8, 1.8 Hz, H_{ortho}), 7.81 (t, 1 H, J = 1.8, H_{ortho}), 11.67 (br s, 2 H, 2 × NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.3 (CH), 125.3 (CH), 130.9 (2 × CH), 131.2 (C), 133.3 (C).

LRMS (EI): m/z = 273 (M^+, 26), 209 ($M^+ - SO_2$, 5), 174 ($M^+ - C_2H_4N_5$, 3), 111 ($C_6H_4Cl^+$, 34), 98 ($C_2H_4N_5^+$, 100).

Anal. Calcd for $C_8H_8ClN_5O_2S$: C, 35.1; H, 3.0; N, 25.6; S, 11.7. Found: C, 35.3; H, 2.7; N, 25.9; S, 11.5.

_N_-(5-Amino-1_H_-[1,2,4]triazol-3-yl)-4-bromobenzenesulfonamide (1f)

White solid; mp 320–321 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.85 (br s, 2 H, NH_2), 7.70 (s, 4 H_{arom}), 11.55 (br s, 1 H, NH), 11.82 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 125.6 (C), 128.4 (C), 132.5 (4 × CH).

LRMS (EI): *m*/*z* (%) = 318 (M^+, 14), 254 ($M^+ - SO_2$, 5), 156 ($C_6H_4Br^+$, 30), 98 ($C_2H_4N_5^+$, 100).

Anal. Calcd for $C_8H_8BrN_5O_2S$: C, 30.2; H, 2.5; N, 22.0; S, 10.1. Found: C, 30.45; H, 2.2; N, 22.3; S, 10.3.

_N_-(5-Amino-1_H_-[1,2,4]triazol-3-yl)naphthalene-2-sulfonamide (1g)

Pale yellow solid; mp 308–309 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.86 (br s, 2 H, NH_2), 7.58–7.67 (m, 3 H_{arom}), 7.83 (dd, 1 H_{arom}, *J* = 8.4, 1.6 Hz), 7.96–8.08 (m, 3 H_{arom}), 8.45 (s, 1 H, H-1), 11.64 (br s, 2 H, 2 × NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 122.4 (CH), 125.6 (CH), 127.2 (CH), 127.7 (CH), 128.0 (C), 128.7 (CH), 128.9 (CH), 131.7 (C), 133.7 (C).

LRMS (EI): *m*/*z* (%) = 289 (M^+, 26), 225 ($M^+ - SO_2$, 18), 191 ($M^+ - C_2H_4N_5$, 6), 127 ($C_{10}H_7^+$, 100), 98 ($C_2H_4N_5^+$, 40).

Anal. Calcd for $C_{12}H_{11}N_5O_2S$: C, 49.8; H, 3.8; N, 24.2; S, 11.1. Found: C, 49.5; H, 3.7; N, 24.3; S, 10.5.130

_N_-(5-Amino-1_H_-[1,2,4]triazol-3-yl)-2,4,6-triisopropylbenzenesulfonamide (1h)

White solid; mp 312–314 °C (dec.) [Lit.[3] mp 314 °C (dec.)].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 [d, 12 H, *J* = 6.8 Hz, 2 × CH(C*H*$_3$)$_2$], 1.17 [d, 6 H, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$], 2.85 [septet, 1 H, *J* = 7.0, C*H*(CH$_3$)$_2$], 4.38 [br m, 2 H, 2 × C*H*(CH$_3$)$_2$], 5.79 (br s, 2 H, NH_2), 7.11 (s, 2 H_{arom}), 11.22 (br s, 1 H, NH), 11.65 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.2 (2 × CH_3), 25.4 (4 × CH_3), 29.1 (2 × CH), 34.0 (CH), 123.5 (2 × CH), 148.7 (C), 151.0 (C).

LRMS (EI): *m*/*z* (%) = 365 (M^+, 21), 322 (M^+ – *i*-Pr, 5), 301 ($M^+ - SO_2$, 1), 267 ($M^+ - C_2H_4N_5$, 43), 203 ($M^+ - C_2H_4N_5 - SO_2$, 14), 98 ($C_2H_4N_5^+$, 12).

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