Regioselective synthesis of heterocyclic N-sulfonyl amidines from heteroaromatic thioamides and sulfonyl azides

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Abstract

N-Sulfonyl amidines bearing 1,2,3-triazole, isoxazole, thiazole and pyridine substituents were successfully prepared for the first time by reactions of primary, secondary and tertiary heterocyclic thioamides with alkyl- and arylsulfonyl azides. For each type of thioamides a reliable procedure to prepare N-sulfonyl amidines in good yields was found. Reactions of 1-aryl-1,2,3-triazole-4-carbothioamides with azides were shown to be accompanied with a Dimroth rearrangement to form 1-unsubstituted 5-arylamino-1,2,3-triazole-4-N-sulfonylcarbimidamides. 2,5-Dithiocarbamoylpyridine reacts with sulfonyl azides to form a pyridine bearing two sulfonyl amidine groups.

Introduction

The biological activity, rich chemistry and technically useful properties of heterocyclic compounds have made them a focal point of science and industry over the years. Heterocyclic compounds including azoles and azines have been found in natural products, and they are included in the structures of nucleic acids, vitamins, antibiotics and in many types of synthetic drugs [1-12]. N-Sulfonyl amidines have received considerable attention because they exhibit various types of pharmaceutical properties and biological activities [13-21] and also have been used as interesting building blocks in organic synthesis [17-20] (Figure 1).

An N-sulfonyl amidine was recently found to be a key group in acid–base-induced rearrangements of 1,2,3-triazoles and thiadiazoles [22]. A variety of methods have been developed for the synthesis of N-sulfonyl amidines. The most commonly used methods to prepare these compounds include the Cu-catalyzed multicomponent reaction of alkynes, sulfonyl azides and amines [23-31], the reaction of thioacetamide derivatives and cyclic thioamides with sulfonyl azides [22,32,33], the chlorophosphite-mediated Beckmann reaction of oximes with p-toluenesulfonyl azide [34], the sulfonyl ynamide rearrangement by treatment with amines [35], the sodium iodide...
catalyzed reaction of sulfonamide with formamide [36], and the condensation of sulfonamide derivatives with DMF–DMA [37].

A few representatives of N-sulfonyl amidines of heteroaromatic acids have been prepared and applied [22,32,38-40]. However, no efficient and general method to prepare a series of heterocyclic N-sulfonyl amidines has been elaborated so far. A new approach to N-sulfonyl amidines has been published recently, based on the reaction of thioamides with sulfonyl azides [33,41,42] (Figure 2). This method was used successfully for the synthesis of N-sulfonyl amidines of aliphatic acids and benzoic acid, including bio-

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**Figure 1:** Examples of biological activity and interesting chemical reactivity of N-sulfonyl amidines.

**Figure 2:** Data on the synthesis of N'-sulfonylazole-4-carboximidamides.
logically active compounds. On the other hand, reactions of thioamides with electrophilic reagents have often been used for the synthesis of various types of sulfur containing heterocyclic compounds [43-47]. This gives some promise to the development of a general and efficient method for the synthesis of N-sulfonyl amidines of heteroaromatic acids based on the reaction of heterocyclic thioamides with highly electrophilic sulfonyl azides.

With the purpose of the synthesis of heterocyclic N-sulfonyl amidines bearing various heteroatoms in the ring, namely nitrogen, sulfur and oxygen atoms, we have studied reactions of thioamides of 1,2,3-triazole-, isoxazole-, thiazolecarboxylic acids and 2,5-dithiocarbamoylpyridine with sulfonyl azides. Due to the high dipole moment, the presence of electronegative heteroatoms bearing electron lone pairs, one could propose alternative reactions which might make it difficult to find a general regioselective procedure for the synthesis of the target molecules in good yields. To the best of our knowledge, there are no examples for the synthesis of N-sulfonyl amidines of heteroaromatic acids through this reaction so far.

Results and Discussion

1-Alkyl-1,2,3-triazole-N-sulfonyl amidines

Since 1,2,3-triazole derivatives exhibit valuable biological and technical properties, and take part in various ring transformations and rearrangements [48-51], we decided to study reactions of 1-alkyl-1,2,3-triazole-4-carbothioamides 1a–d with aryl- and alkylsulfonyl azides 2a–f with, with the goal of affecting a “iminosulfonylation” (Scheme 1).

The thioamides 1a–d were prepared from the corresponding amides 4a–d by treatment with phosphorus decasulfide (Scheme 1). It is worth noting that amides of 1-alkyl-1,2,3-triazole-4-carboxylic acids are poorly represented in the literature and the methods of their preparation require the addition of alkyl azides to acetylene carboxylic esters and reactions of 2-diazomalonates with aliphatic amines [40,52]. The first approach leads to a mixture of two regioisomers and the second method involves the use of explosive diazo compounds. Therefore, such compounds are better prepared by a recently found method in our laboratory which includes the reaction of 4-acetyl-1,2,3-triazole 5a–d with aniline followed by a Cornforth rearrangement of the 1,2,3-triazole ring [52]. Alkyl- (2a,b) and arylsulfonyl (2e–g) azides were prepared, respectively, from the corresponding sulfonyl chlorides and sodium azides according to published methods (Figure 3) [53].

We have found that 1-butyl-1,2,3-triazole-4-carboxothioamide 1c reacts well with benzenesulfonyl azide 2c in various solvents to form the desired 1-butyl-1,2,3-N-sulfonyl amidine 3n in diverse solvents such as n-butanol, n-propanol, toluene, ethanol, water and even under solvent-free conditions (see Table 1 for the yields and other circumstances).

From these data we can conclude that the yield of the final product is optimal for the reaction under solvent-free conditions. 1-Butyl-1,2,3-triazole 1c reacts faster than 1,2,3-triazole-4-carbothioamide 1f while using a lower amount of a sulfonyl azide (Table 1, entry 11 and Table 2, entry 14). Thus solvent-free conditions, a temperature of 88 °C and a thioamide/azide ratio of 1:2.5 are optimal to prepare N-sulfonyl amidine 1c (entry 11, Table 1).

Next, these optimized conditions were used for the synthesis of a small library of 1-alkyl-1,2,3-triazoles 3a–s (Scheme 2).

The reaction can be applied without problems to various alkyl substituents in position 1 of the 1,2,3-triazole ring from methyl to decyl and benzyl, goes well with alkylsulfonyl azides and arylsulfonyl azides that were 4-substituted with both electron-withdrawing and electron-donating substituents.

5-Arylamino-1,2,3-triazole-N-sulfonyl amidines

To further expand the scope of the reaction we continued studying the reaction of 1-aryl-1,2,3-triazole-4-carbothioamides 1e–h with aryl- and alkylsulfonyl azides 2a,c,f.

We have found that thioamide 1e did react with benzenesulfonyl azide 2c neither in water, ethanol nor in the absence of a solvent, conditions that were successfully used in the synthesis
Table 1: Optimizations of the reaction conditions for the reaction of thioamide 1c with phenylsulfonyl azide 2c.

| Entry | Solvent | T (°C) | 2c (equiv) | t (h) | Yield (%) |
|-------|---------|--------|------------|-------|-----------|
| 1     | n-BuOH  | 117    | 5          | 21    | 23        |
| 2     | n-BuOH  | 100    | 5          | 12.7  | 75        |
| 3     | n-PrOH  | 97.4   | 5          | 12.7  | 80        |
| 4     | n-PrOH  | 97.4   | 2.5        | 12.7  | 63        |
| 5     | toluene | 105    | 5          | 12.7  | 26        |
| 6     | water   | 100    | 5          | 12.7  | 61        |
| 7     | ethanol | 78.5   | 5          | 21    | 74        |
| 8     | neat    | 88     | 1.2        | 12.7  | 34        |
| 9     | neat    | 88     | 5          | 4     | 86        |
| 10    | neat    | 55     | 5          | 24    | 63        |
| 11    | neat    | 88     | 2.5        | 5     | 87        |

Table footnotes: aReaction conditions: 0.18 mmol of 1c, solvent (1 mL); bisolated yield.

On the other hand, we have found the formation of a new product 3t in low yield together with the starting compound 1e and the product of its rearrangement to 5-(4-nitrophenyl)aminotriazole 1j [54], when the reaction was carried out in n-butanol at 105 °C (Table 2). Therefore, we can conclude that compound 3t was the product of a tandem reaction involving first the rearrangement of thioamide 1e to 1j followed by iminosulfonylation of the latter to form amidine 3t (Table 2).

To obtain higher yields of sulfonyl amidines we decided to prepare 5-arylamino-1,2,3-triazole-4-carbothioamide 1j by rearrangement of triazole 1e [54] and carried out an optimization with variations of the solvent, temperature and various additives (Table 2). We have shown that optimal conditions include the use of n-propanol, a temperature of 97 °C and a ratio of thioamide 1j and azide 2c of 1:7 which allowed to prepare the desired compound 3t in 78% (Table 2).

With the optimal conditions in hand we prepared a series of N-sulfonyl amidines 3t–aa in good yields (Scheme 3). Thus, a library of N-sulfonyl amidines bearing differently substituted 1,2,3-triazoles was successfully prepared. Among them are compounds bearing an NH-unsubstituted 1,2,3-triazole ring of 1-alkyl-1,2,3-triazole-4-N-sulfonylimidamides 3a–s (Scheme 2).
which gives extra possibilities for the modification of the molecules by the reaction with electrophilic reagents to prepare new compounds of this series [55] (Scheme 3).

To show the practical convenience of the developed method we tried to synthesize these compounds in a one-pot procedure starting from readily available 1-aryl-1,2,3-triazoles 1f, g, t and sulfonyl azides 2c, f (Table 3). Thioamides 1f, g, t were converted to 5-arylamino-1,2,3-triazoles 1i–k by heating at reflux in n-propanol in the presence of DBU and these rearranged thioamides were then treated with sulfonyl azide 2c, f and kept at the same temperature for 17–31 h. After flash column chromatography, pure N-sulfonyl amidines 3t, u, x were isolated in 41–65 % yield. The data of Table 3 demonstrates that the yields of sulfonyl amidines 3t, u, x are higher when we used the one-pot protocol in comparison with the two-step method. Furthermore, the one-pot procedure is obviously more simple and less time consuming.
Table 2: Synthesis and optimization of the reaction conditions for the reaction of thioamide \textit{1j} with phenylsulfonyl azide (2\textit{c})$^a$.

| Entry | Solvent (additive) | $T$ (°C) | 2\textit{c} (equiv) | $t$ (h) | Yield$^b$ (%) |
|-------|--------------------|----------|----------------------|--------|----------------|
| 1     | $n$-BuOH           | 105      | 1                    | 17.5   | 33             |
| 2     | $n$-BuOH           | 105      | 7                    | 17.5   | 76             |
| 3     | $n$-BuOH (Cs$_2$CO$_3$, 10 mol %) | 105 | 5 | 5 | no reaction |
| 4     | $n$-BuOH (Cul, 10 mol %) | 105 | 5 | 5 | no reaction |
| 5     | $n$-PrOH           | 88       | 5                    | 17.5   | 43             |
| 6     | $n$-PrOH           | 97.4     | 5                    | 17.5   | 52             |
| 7     | $n$-PrOH           | 97.4     | 7                    | 17.5   | 78             |

$^a$Reactions conditions: 0.45 mmol of thioamide \textit{1j}, solvent (3 mL); $^b$ Isolated yield.

Scheme 3: Scope of the reaction of 5-arylamino-1,2,3-triazole-4-carbothioamides \textit{1i}–\textit{l} with azides \textit{2a},\textit{c}–\textit{f}.
Table 3: Yields of triazoles 3t,u,x following a one-pot procedure\(^a\) compared to the yields involving the isolation of 5-arylamino-1,2,3-triazoles 1i–k.

| Entry | Thioamide 1 | Azide 2 | Product 3 | Yield of 3, % (time) |
|-------|-------------|---------|-----------|---------------------|
|       | 1t          | 2f      | 3x        | 49 (17.5 h)         |
|       | 1g          | 2c      | 3u        | 41 (31 h)           |
|       | 1f          | 2f      | 3t        | 65 (31 h)           |

\(^a\) (0.60–0.65 mmol), DBU (0.63–0.65 mmol), 2 (3.56–4.0 mmol), HOAc (1 mL).

2-Aminothiazole-4-N-sulfonyl amidines

In spite of the presence of a nucleophilic amino group capable to react with sulfonyl azide to form an azide group, the reaction of azides 2 occurred selectively to the thioamide group of compound 1m.

Thus, similar to the reaction of 5-arylamino-1,2,3-triazole-4-carbothioamides 1i–l, the reaction of the primary thioamide of 2-aminothiazole-4-carboxamide (1m) with sulfonyl azides 2a,c is successful in \(n\)-propanol at reflux temperature, to afford \(N\)-sulfonyl amidines 3ab and 3ac bearing a 2-aminothiazole ring in very good yields (Scheme 4).

Scheme 4: Synthesis of 2-aminothiazole-4-N-sulfonyl amidines.

3-Methyl-5-phenyl-isoxazole-4-N-sulfonyl amidines

The primary thioamide 1n containing an isoxazole ring was shown to react with mesyl azide or arylsulfonyl azides in \(n\)-propanol at reflux temperature to form the \(N\)-sulfonyl amidines 3ad–ag in 49–76% yields (Scheme 5).

The reaction takes place also in the absence of a solvent, albeit in lower yields. We have found that secondary thioamide 1o does not react with sulfonyl azides 2a,c either in \(n\)-propanol or in the absence of a solvent. On the other hand, we have found that the reaction can occur in \(n\)-butanol at 118 °C to form compounds 3ah–ai in low yields (38–45%) accompanied with the formation of tar-like products.

2,5-Bis((N-sulfonylamidino)pyridines

Bis(thioamide) 1p containing a pyridine ring was found to react with sulfonyl azides 2a,c–f either in boiling propanol or in the absence of a solvent to form compounds 3aj–an bearing two \(N\)-sulfonyl amidine fragments connected to a pyridine linker. The solvent-free protocol includes the use of a lower amount of azide 2d,c,f (2.5 equiv) in comparison with the reaction in \(n\)-propanol (4 equiv of azide) to afford the desired products in the same yield and therefore was selected as the method of choice for the synthesis of 3aj–an (Scheme 6). The synthesis of complexes of bis(sulfonyl amidines) 3aj–an with metals is in progress.

\(^{1}\)H and \(^{13}\)C NMR spectra including 2D HMBC and HSQC experiments of compounds 3a–an, as well as high-resolution mass spectra are consistent with the proposed structures. Carbon signals of the amidine groups of compounds 3 appear at
Scheme 5: Synthesis of N-sulfonyl amidines of isoxazolylcarboxylic acid.

Scheme 6: Synthesis of bis(sulfonyl amidines) 3aj–an.

Conclusion

Because of the observed evolution of nitrogen and sulfur in every reaction of heterocyclic thioamides and sulfonyl azides it is logical to propose the formation of a thiatriazole ring via [3 + 2] cycloaddition of the azide group and the C=S moiety of the thioamide group (Scheme 7).

The formation of nitrene-like products was excluded because of the high selectivity of the process, where only the thioamide group takes part, even with heterocyclic rings that contain other nucleophilic centers, and in one case, an amino group. Thiatriazoles are known to be unstable compounds that readily evolve nitrogen and sulfur upon heating [56].

Conclusion

We have shown that the reaction of sulfonyl azides with thioamides can serve as the basis for a general and efficient method for the regioselective synthesis of N-sulfonyl amidines of azolyl and pyridine carboxylic acids. The most promising aspect for organic synthesis and green chemistry is a solvent-free process which was successfully applied to prepare sulfonyl amidines containing pyridine and isoxazolyl rings and 1-alkyl-1,2,3-triazole-4-N-sulfonylamidino-1,2,3-triazoles. The 1-alkyltriazole thioamides are the most active in the solvent-free method due to their low melting points and good solubility in alkyl- and arylsulfonyl azides. Conversely, thioamides containing 5-arylamino-1,2,3-triazole and 2-aminothiazole rings are not soluble in sulfonyl azides and could be transformed to the corresponding N-sulfonyl amidines by reactions in 1-propanol via two- or one-pot procedures. Pyridine-2,6-dithioamide was shown to react with mesyl and arylsulfonyl azides to form 154.1–159.7 ppm which is close to 156 ppm which is the value found for N-sulfonyl amidines of 1,2,3-thiadiazole-4-carboxylic acid prepared by another method [22] and was clearly different from the thioamide carbon signal at 185–187 ppm in the $^{13}$C NMR spectra of starting materials 1. A final proof of the structures of the prepared compounds comes from the X-ray data for 3ej,ta, and ag (Schemes 2, 3, and 5). Moreover, the X-ray data reveal the existence of N-sulfonyl amidines 3ej in the E-isomeric form and N-sulfonyl amidine 3ag in Z-isomeric form. The existence of the latter in the Z-isomeric form can be explained by steric hindrance between the phenyl and the arylsulfonyl groups.

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pyridine derivatives bearing two N-sulfonyl amidine moieties in excellent yield. Depending on the structure of the heterocycle the N-sulfonyl amidines exist in either E- or Z-isomeric forms.

Experimental
X-ray diffraction study
X-ray analyses were accomplished on an Xcalibur 3 diffractometer using the standard procedure (graphite-monochromated Mo Kα irradiation, ω-scanning with step 1°, T = 295(2) K (see Supporting Information File 3). Using Olex2 [57], the structures were solved with the Superflip [58] structure solution program using charge flipping and refined with the ShelXL [59] refinement package using least squares minimization. Deposition numbers for compounds 3e (2020829), 3t (2020831) and 3ag (2020830), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information
Supporting Information File 1
Full experimental details and characterization data of all new compounds, crystal data and structure refinement for 3e, 3t, and 3ag.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-243-S1.pdf]

Supporting Information File 2
Copies of NMR spectra of all new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-243-S2.pdf]

Supporting Information File 3
Crystallographic information files for compounds 3e, 3t and 3ag.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-243-S3.zip]

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