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A One-Pot Synthesis of Sulfonyl Amidinesvia Three-Component Reaction Under Mild and Solvent-Free Conditions

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Abstract

A convenient one-pot synthetic protocol for the preparation of sulfonylamidines has been developed. The procedure combines three-component reaction of sulfonyl-azide, methyl propiolate and secondary cyclic amine coupling in one sequence without any solvent or catalyst and at room temperature. The reaction proceeds smoothly and a variety of desired sulfonylamidines were obtained in moderate to good yields. This protocol has synthetic advantages in terms of low environmental impact and veryshort reaction time.

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Introduction

Multicomponent reactions (mcrs) are a powerful tool for the synthesis of complex molecules with broad structural diversity in a single operation[1].These reactions combine at least three or more reactants in a one-pot reaction to form a new product that incorporates structural features of each reagent.[2] Compared to conventional multistep organic syntheses, this strategy offers several other advantages besides atom economy, such as higher overall yields, shorter reaction times, environmentally benign milder reactions, and easiness of procedure.[3] mcrs have played a central role in the development of modern synthetic methodology for biologically active compounds, bioactive heterocycles and natural products.[4]

Heterocyclic compounds constitute the largest and most varied family of organic compounds significant to almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry.[5] Amidines,the dinitrogen analogs of carboxylic acids, are widely used in medicinal chemistry,[6]coordination chemistry,[7]and synthetic chemistry.[8] They are important units in chemistry for the synthesis of various diversified nitrogen heterocycles[9] e.g., pyrroles,[10] triazoles,[11] pyridines,[12] pyrimidines,[13] thiadiazines[14] and triazines.[15] In addition, these compounds are found in numerous natural bioactive products and are identified as important pharmacophores.[16]

Indeed, a broad range of nitrogen compounds containing an amidine moiety have interesting Biologicalproperties, such as anti inflammatory,[17] antiparasitic,[18] antiplatelet,[19] antimalarial,[20] anti-cancer[17,21] and antimicrobial activities,[22]etc. The sulfonylamidine units also show broad-spectrum biological activities. In order to illustrate the importance of the sulfonylamidine motifs in the field of pharmaceutical chemistry, a few examples of molecules with biological and therapeutic activities (antitumor,[23] antiprolifera-tive,[24] antibacterial,[25] and antiresorptive[26]) incorporating them have been selected in figure 1.

There are several strategies described in the literature for the synthesis of amidines.[27]The most common method is based on the simple functional group transformation from some precursors such as nitriles, [28] amides.[29] Other methods for their preparation include the reduction of amidoxime,[30]the cycloaddition-decarboxylation of isocyanates and nitrones.[31] Also, they were prepared by the reductive functionalization of carboxamides (*via* enamines) into sulfonylfor-mamidines.[32] Furthermore, they are prepared using the 1,3-dipolar cycloaddition reaction between the enaminoesters and sulfonyl azides,[33] etc. Recently, numerous methods for the synthesis of sulfonylamidines have been reported.[34]Among various mcrs developed, the Cu-catalyzed three-component coupling reactions of a terminal alkyne, a sulfonylazide and with a third component, like amine, alcohol or water are one of the most powerful strategies for forming sulfonylamidines, N-sulfonylimidates, and sulfonamides, respectively.[35]A highly efficient copper-catalyzed one-pot synthesis of *N*-sulfonylamidines has been described by Chang and co-workers *via* the coupling of a sulfonylazide, an alkyne and an amine.[35, 36] Many other copper catalyzed three-component reaction, involving a sulfonylazide, an alkyne and an amine, are performed under widely differing conditions have been reported by Wang's group[37] and others.[38] However, these approaches to synthesize sulfonylamidines suffered from some disadvantages including stepwise synthesis, harsh reaction conditions, long reaction times and requirement of inert atmosphere, the use of catalyst or expensive reagents and hazardous organic solvents.

Therefore, the development of a mild, simple, fast and novel method with attractive features such as easily accessible starting materials, mild reaction conditions, and non-toxic side products to generate structural diversity sulfonylamidines is still desirable because of their biological significance. As a continuation of our interest in developing new green synthetic methods of sulfonyl amidines,[39] herein we report a facile, rapid andpractical synthesis of sulfonylamidines, potentially bioactive, *via* a MCR performed in air, coupling of arenesulfonylazides with methyl propiolate and secondary cyclic amines using solvent-free conditions and without requiring any catalyst or additive.

Experimental

All reagents and solvents were purchased from commercial suppliers and were used without further purification. Melting points were determined with a Kofler apparatus and they are uncorrected. 1H (300

mhz) and 13C (75 mhz), NMR spectra were recorded using a Bruker AC300 sptaken ectrometer using cdcl3.Infrared spectra (IR) were on a Nicolet IRFT IR 200 spectrometer, and were obtained as solids in kbr. Peaks are reported in cm-1. High-resolution mass spectra (MS) were obtained at 2.8kv electrospray voltage, 20 V voltage orifice, and flow of nebulizing gas (nitrogen): 100 L/h.

Atmospheric pressure ionization (API) and electrospray (ESI) mass spectra were recorded on a SYNAPTG2 HDMS spectrometer (Waters). Elemental analyses were performed by apparatus CHNS

General Procedure for Preparing Sulfonylazides

The sulfonyl azides1 were prepared according to the procedure of the literature[40] which was modified as follows: sulfonyl chloride (30 mmol) in acetone (25 ml) was added drop wise to a solution of sodium azide (33 mmol) in 10ml of ethanol (96%) at room temperature. Upon addition the solution turns an orange color with nacl precipitate was seen. After stirring for 15 hours the precipitate was filtered off and the solvent was evaporated. The residue was taken up with water and extracted with 25 ml dichloromethane. The organic layer was dried over anhydrous mgso4, filtered and the solvent was evaporated under reduced pressure to give the desired sulfonylazide

General Procedure For Synthesis Of Sulfonylamidines Under Mild And Solvent-Free Conditions

Sulfonylazide1 (1 mmol,1 equiv.), methyl propiolate (1 mmol, 1 equiv.)Andamine2(1 mmol,1 equiv.) Wassuccessivelyadded to a flask at room temperature, after that a precipitate was formed,a pure product was obtained by recrystallization in etoh followed by simple filtration.

Results And Discussion

Sulfonyl amidines3-5 are obtained by a direct three-component reaction of arenesulfonylazide, methyl propiolate with secondary cyclic amines (Scheme 1).

The structure of synthesized sulfonylamidines 3-5 was confirmed mainly by a combination of the usual spectroscopic methods (IR, ^{1}H, ^{13}C, DEPT NMR) elemental analysis, and the mass spectra which gave good agreement with the proposed structures.

The reaction conditions for a sequential one-pot procedure were optimized using different solvents, as illustrated in Table 1.

Preliminary experiments were carried out with tosylazide1a, methyl propiolate and morpholine2a. The reactions were performed in various solvents. As can be seen from Table 1, THF, CH_2Cl_2, methanol and toluene afforded low yields (Table 1, entries 1, 3, 5 and 7), whereas the solvents H_2O, $chcl_3$, and DMSO achieved moderate yield (Table 1, entries 2, 6 and 8). The reaction accomplished in ether leads to a good yield (Table 1, entry 4). However, the best yield was obtained in the absence of the solvent (Table 1, entry 9).

To extend the general applicability and the reactivity of this three-component reaction, several substituted sulfonylazides1 bearing electron-donating and electron-withdrawing groups, were reacted with methyl propiolate and secondary cyclic amines (morpholine, piperidine and pyrrolidine) under the optimized conditions in the absence of solvent and without any catalyst, the results are given in Tables 2, 3 and 4.

Arenesulfonylazides were successfully employed as efficient reacting partners in three-component coupling with methyl propiolate and morpholine to afford the corresponding sulfonylamidines (3a-l) which were produced with yields varying from 22 to 89%, spontaneously. The reactions proceeded very efficiently, and led to the formation of the corresponding sulfonylamidines 3a, 3d and 3e in good yields (Table 2, entries 1, 4 and 5) as 89, 84 and 88%, respectively. However, a drastic decrease in yield (32 and 29%) was observed with the benzene sulfonylazide and the *para*-ethylbenzenesulfonylazide (Table 2, entries 2 and 3). On the other hand, the electron with-drawing *para*-nitro was found to be more reactive than the *ortho*-nitro and the *meta*-nitrobenzenesulfonylazides (Table 2, entries 5-7) with 88, 41 and 54%, respectively. The reaction was also compatible with the presence of the halogen groups. Thus, the bromo and iodo groups led to the desired products 3j, and 3k with better yields compared to the fluoro and chloro groups which led to the compounds 3h and 3i (Table 2, entries 8-11) with 72 , 64, 22 and 42%, respectively. It is noted that the disulfonylamidine3l was obtained with a yield of 66%

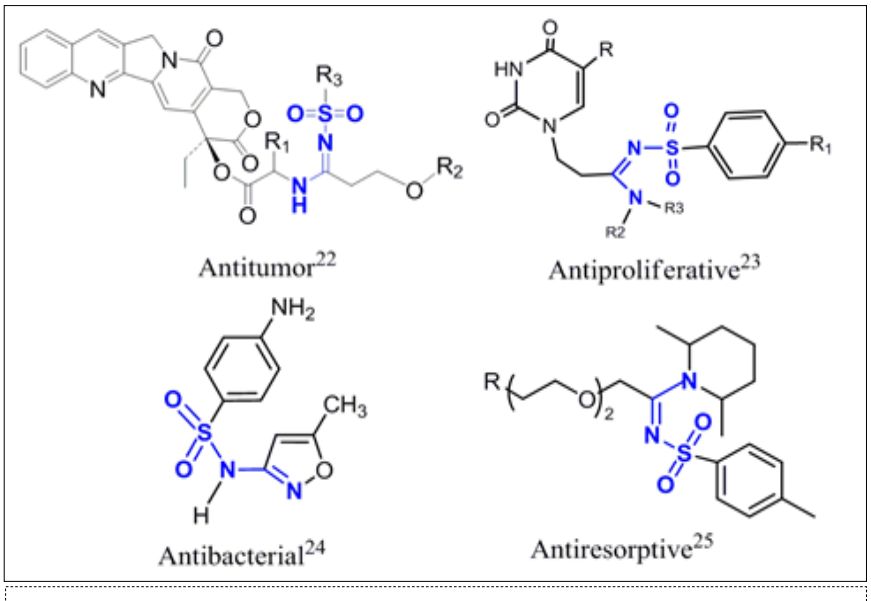
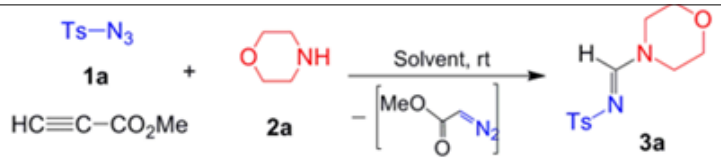


Figure 1. Selected examples for bioactive sulfonylamidines

Scheme 1. One pot synthesis of sulfonylamidines 3-5

Table 1. Optimization of the reaction conditions for the three-component reactions of tosylazide1a, methyl propiolate and morpholine2a.



Entry	Solvent	Time	Yield(%) [b]
1	MeOH	1h 30 min	23
2	H_2O	1h	46
3	THF	20h	16
4	Et_2O	1h 30 min	87
5	CH_2Cl_2	1h	23
6	$CHCl_3$	1h 30 min	46
7	toluene	1h 30 min	8
8	DMSO	3h	52
9	**Solvent-free**	**Spontaneous**	**89**

[a]Reaction conditions: tosylazide**1a** (1 mmol, 1 equiv.), methyl propiolate (1 mmol, 1 equiv.), and morpholine**2a** (1 mmol, 1 equiv.), [b]Isolated yield after recrystallization in ethanol followed by simple filtration.

(Table 2, entry 12).

In addition, the system was applied to other amines. The results obtained for the synthesis of sulfonylamidines (4a-i) from piperidine are given in the Table 3

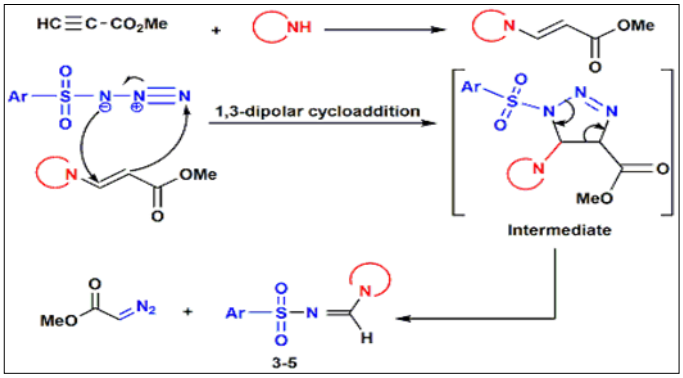
Using piperidine as nucleophilic partner, we evaluated the ability to perform the three-component reaction. This reaction sequence generated the corresponding sulfonylamidines (4a-i) with yields ranging from 11 to 81%. The best yield was obtained from the para-nitro benzenesulfonylazide. Indeed, the para-nitro benzenesulfonylazide has a decisive influence on the successful formation of 4c (Table 3, entry 3) as 81%. The ortho-nitro and the meta-nitro benzenesulfonylazide were also examined as electron with-drawing source and gave the targeted products 4d and 4e in moderate yields (Table 3, entries 4 and 5) as 51 and 44%. The presence of either electron-donating groups (Me) or (2,4,6-triisopropyl) on benzenesulfonylazide provides almost similar yields (Table 3, entries 1 and 2) around 40%. The arenesulfonylazides containing a halogen group reacted with piperidine and methyl propiolate were unsuccessful. The corresponding products 4f-h were obtained in weak yields (Table 1, entries 6-8), with 14, 13 and 11% yields, respectively. The benzene-1,3-disulfonylazide give low yield of the desired product 4i (Table 3, entry 9) with a 28% yield.

Difference in reactivity was also observed when pyrrolidine was used. The results obtained for the synthesis of sulfonylamidines (5a-j) are shown in the Table 4.

Next, we performed to prepare sulfonylamidines by way of the pyrrolidine according to the same sequence and under the same conditions as the previous reactions. This reaction produces the corresponding sulfonylamidines 5a-j with yields ranging from 10 to 51%. When the reaction was run with the tosylazide and benzenesulfonylazide the sulfonylamidines 5a and 5b were isolated in only 15 and 10%, respectively (Table 4, entries 1 and 2). In other hand, the 2,4,6-triisopropyl, bulky and strongly electron-withdrawing group, showed low reactivity leading to relatively moderate yield of 44% for the sulfonylamidine 5c (Table 4, entry 3). It is note that substitution of the benzenesulfonylazide by nitro group in the ortho or meta position on the phenyl ring provided the desired sulfonylamidines 5d and 5e in moderate yields (Table 4, entries 4 and 5) as 43%. Also, the benzene-1,3-disulfonyl azide give the disulfonylamidine 5i with an average yield of 51% (Table 4, entry 10). However, when the electron donor substituent has been used such as halogen groups (fluoro, chloro, bromo and iodo) low yields were obtained ranging from 22-33% in this case (Table 4, entries 6-9).

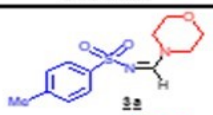
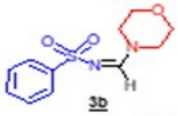
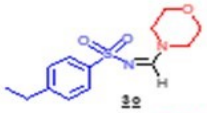
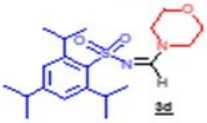
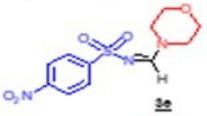
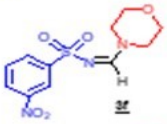
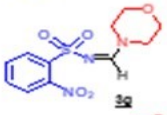
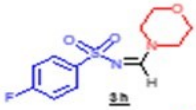
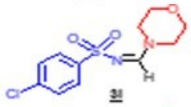
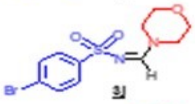
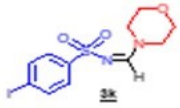
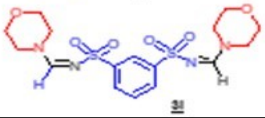
On the basis of our experimental results, together studies in literature [41], a possible reaction mechanism for the formation of sulfonylamidines is proposed in Scheme 2.

First the secondary cyclic amine reacts with methyl propiolate through a hydroamination reaction to afford corresponding enamine. Then, the formed enamine reacts with arenesulfonylazide to yield the unstable $\Delta^2$1,2,3-triazolineintermediate which then release one molecule of methyl diazoacetate to provide



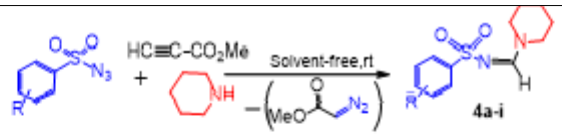
Scheme 2. Proposed mechanism for the synthesis of compounds 3-5.

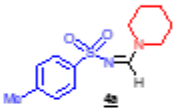
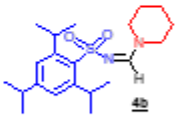
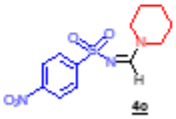
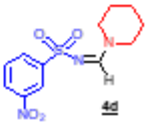
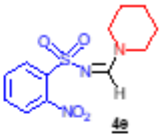
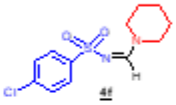
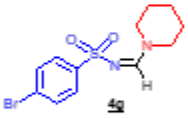
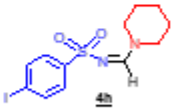
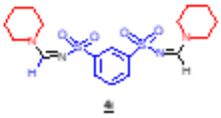
Table 2. Sulfonyl amidines3 prepared from methyl propiolate, arenesulfonylazides and morpholine[a]

Entry	R	Product	Yield(%)[b]
1	*p*-Me		89
2	H		32
3	Et		29
4	2,4,6-triiso propyl		84
5	*p*-NO_2		88
6	*m*-NO_2		41
7	*o*-NO_2		54
8	*p*-F		22
9	*p*-Cl		42
10	*p*-Br		72
11	*p*-I		64
12[c]	*m*-sulfonylazide		66

[a]Reaction conditions: arenesulfonylazide**1** (1 mmol, 1 equiv.), methyl propiolate (1 mmol, 1 equiv.), and morpholine**2a** (1 mmol, 1 equiv.), [b]Isolated yield after recrystallization in ethanol followed by simple filtration, [c]Benzene-1,3-disulfonyl azide (1 mmol, 1 equiv.), methyl propiolate (2 mmol, 2 equiv.), and morpholine**2a** (2 mmol, 2 equiv.).

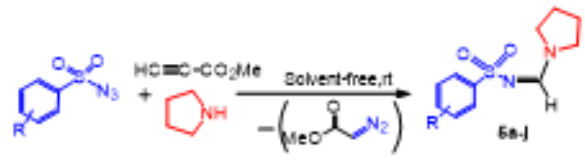
Table 3. Sulfonyl amidines4 prepared from methyl propiolate, arenesulfonylazides and piperidine[a]

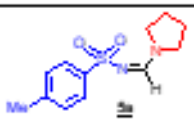
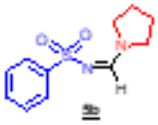
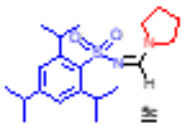
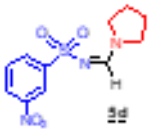
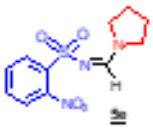
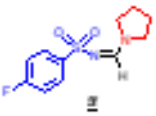
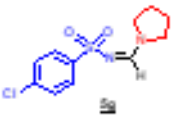
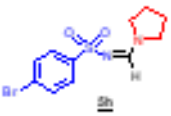
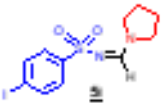
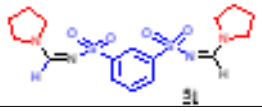


Entry	R	Product	Yield(%)[b]
1	*p*-Me		46
2	2,4,6-triiso propyl		42
3	*p*-NO_2		**81**
4	*m*-NO_2		51
5	*o*- NO_2		44
6	*p*-Cl		14
7	*p*-Br		13
8	*p*-F		11
9[c]	*m*- sulfonylazide		28

[a]Reaction conditions: arenesulfonylazide**1** (1 mmol, 1 equiv.), methyl propiolate (1 mmol, 1 equiv.), and piperidine **2b** (1 mmol, 1 equiv.), [b]Isolated yield after recrystallization in ethanol followed by simple filtration, [c]Benzene-1,3-disulfonyl azide(1 mmol, 1 equiv.), methyl propiolate (2 mmol, 2 equiv.), and piperidine **2b** (2 mmol, 2 equiv.)

Table 4. Sulfonyl amidines5 prepared from methyl propiolate, arenesulfonylazides and pyrrolidine[a]



Entry	R	Product	Yield(%)[b]
1	*p*-Me		15
2	H		10
3	2,4,6-triiso propyl		44
4	*m*-NO_2		43
5	*o*-NO_2		43
6	*p*-F		24
7	*p*-Cl		30
8	*p*-Br		26
9	*p*-I		22
10[c]	*m*-sulfonylazide		51

[a]Reaction conditions: arenesulfonylazide**1** (1 mmol, 1 equiv.), methyl propiolate (1 mmol, 1 equiv.), and pyrrolidine **2c** (1 mmol, 1 equiv.), [b]Isolated yield after recrystallization in ethanol, followed by simple filtration. [c]Benzene-1,3-disulfonyl azide(1 mmol, 1 equiv.), methyl propiolate (2 mmol, 2 equiv.), and pyrrolidine**2c** (2 mmol, 2 equiv.)

the expected sulfonylamidines 3-5. It should be noted that the nature of substituents of arenesulfonylazides and the cyclic secondary amine structure has a great influence on the yield of the reaction.

Conclusion

In conclusion, we have developed a fast, efficient, easy, and practical three-component reaction of arenesulfonylazides, methyl propiolate and secondary cyclic amines to produce sulfonylamidines. The reactions were performed without any solvent or catalyst, at room temperature, very short reaction time and with moderate to good yields. Compared to previously other reported synthesis of sulfonylamidines, this protocol is highlighted by its simplicity, atom economical nature and green operational method.

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