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Article

Effect of Sulfamic Acid on 1,3-Dipolar Cycloaddition Reaction: Mechanistic Studies and Synthesis of 4-Aryl-*NH*-1,2,3-triazoles from Nitroolefins

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A facile and new metal-free 1,3-dipolar cycloaddition reaction for the synthesis of 4-aryl-*NH*-1,2,3-triazoles from nitroolefins and NaN_3 employing NH_2SO_3H has been developed. Sulfamic acid proved to be an efficient additive in this transformation by inhibiting the formation of triaryl benzene. Mechanistic aspects and key intermediates associated with this transformation have also been characterized by online monitoring of the reaction using electrospray ionization tandem mass spectrometry method (ESI-MS/MS). The protocol emphasizes broad substrate scope for many functionalities, simple reaction conditions such as stability to open air, less reaction time, easy work-up, eco-friendly and with good to excellent yields.

Keywords: bioactive triazoles, electrospray ionization, reaction mechanism, green chemistry

Introduction

The development of drug-like heterocyclic molecules from simple precursors is one of the utmost important and promising area in synthetic organic chemistry. Triazoles are one of these heterocycles known to exist as 1,2,3- and 1,2,4-triazoles according to their position of nitrogen atoms. Particularly, the 1,2,3-triazoles act as an important class of nitrogen rich five-membered heterocycles that are known to exhibit their importance in medicinal chemistry.[1]

Apart from medicinal properties, 1,2,3-triazoles are found to have wide range of industrial applications such as dyes, agrochemicals, materials, corrosion inhibitors and photostabilizers.[2] Huisgen *et al.*[3] have been intensively developing the conventional route for the synthesis of 1,2,3-triazoles which involves the 1,3-dipolar cycloaddition between azides and alkynes. However, these cycloaddition reactions have required high activation energy, temperature, prolonged reaction time and the products turn out to be a mixture of two 1,4- and 1,5-regioisomers. With the intention of controlling the regioselectivity of this reaction and to improve the reaction conditions, several methodologies have been developed by using various transition-metal catalysts.

Originally, Rostovtsev *et al.*[4] and Tornøe *et al.*[5] have independently defined click chemistry in which Cu^I-catalyzed azide-alkyne cycloaddition (CuAAC) allowed the best regioselectivity (1,4-regioisomer). Till date, Cu^I stands out to be the only metal-catalyst for the facile and reliable 1,4-regiospecific azide-alkyne cycloaddition. Further, ruthenium catalyzed azide-alkyne cycloaddition (RuAAC) was also discovered for the synthesis of 1,5-regioisomer.[6] CuAAC is mainly well recognized with quite different catalysts and ligands.[7,8] Since all these protocols needed terminal alkynes and organic azides, thus are limited to the synthesis of *N*1-substituted 1,2,3-triazoles. Several other methods have also been reported, like organo-catalyzed azide-ketone cycloaddition,[9] I_2/TBPB oxidative cyclization of *N*-tosylhydrazones and anilines,[10] Ir-catalyzed azide-alkyne cycloaddition (IrAAC)[11] and metal-free multi-component reactions.[12] However, even after great developments in synthetic organic chemistry, there are only a few methodologies that allow the construction of predetermined moieties in some classes of compounds. In this context, a particular attention in efficient synthetic

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routes for new scaffolds is already practiced in which short or concise routes are needed.

The *NH*-1,2,3-triazoles possess different biological properties like anticancer, antibacterial, etc. This class of compounds is also known to exert its bioactivity through inhibitions of different enzymes like indoleamine 2,3-dioxygenase (IDO), adenosine deaminase (ADA) and h-NK1 antagonist (Figure 1).[13] The difficulty in the deprotection of alkyl or aryl group from the *N*1-substituted 1,2,3-triazole framework poses a challenging task to the researchers for the synthesis of *NH*-1,2,3-triazoles. A good number of 1,2,3-triazoles has been reported in the literature.[14] However, very less attention has been paid to cycloaddition of nitrostyrenes with azide.[15] The methods for the synthesis of *N*-unsubstituted 1,2,3-triazoles are still limited to the cycloaddition of terminal alkyne and hydrazoic acid (*in situ* generated from sodium azide and acid).[16] Amantini *et al.*[17] have reported that tetrabutylammonium fluoride (TBAF) promoted the addition of azides with nitroethenes under solvent-free conditions. Other methods, such as cycloaddition of $TMSN_3$ (trimethylsilyl azide) with alkynes by using Cu^I-catalyst[18] and Pd-catalyzed reaction of vinyl bromides with azides,[19] have been reported. Recently, Quan *et al.*[20] have also reported a method by employing *p*-toluenesulfonic acid for the synthesis of this class of molecules.

In recent years, the use of solid acids as heterogeneous catalyst has attracted interest in synthetic chemistry, one of such heterocatalyst, i.e., sulfamic acid (NH_2SO_3H) has emerged as a promising substitute for conventional Brønsted/Lewis acid as it is a stable, inexpensive, non hygroscopic, non-volatile, non-corrosive and efficient green catalyst. It possesses unique catalytic features related to its zwitterionic nature and displays an excellent activity over a wide range of acid catalyzed organic transformations, like acetalytion, esterification, Biginelli condensation, Beckmann rearrangement, Diels-Alder reactions, Mannich, Hantzsch, Michael and Pechmann reactions.[21] In continuation of our interest in the development of new methodologies related to 1,2,3-triazoles,[22] we herein reported the use of sulfamic acid as a new catalyst for the metal-free 1,3-dipolar cycloaddition reaction from nitroolefins with NaN_3, and the key intermediates associated with this transformation have been characterized by on line monitoring of the reaction by using electrospray ionization tandem mass spectrometry method (ESI-MS/MS).

Experimental

All the starting materials and other reagents were commercially available of the best grade and were used without further purification. All the nitroolefins were prepared according to already known procedures.[23] The progress of the reactions was monitored by thin layer chromatography (TLC), performed on silica gel 60-F_{254} plates. Spots were visualized by UV light. All nuclear magnetic resonance (NMR) spectra were recorded using a Bruker spectrometer. ^1H and ^{13}C NMR spectra were recorded on 300 and 500 MHz spectrometers using tetramethylsilane (TMS) as internal standard. Chemical shifts are reported relative to internal standard (TMS at δ_H 0.00 or $CDCl_3$ at δ_H 7.26 or DMSO-d_6 at δ_H 2.50). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were recorded at 75 and 100 MHz. The following internal reference was used: $CDCl_3$ at δ 77.0 or DMSO-d_6 at δ 39.5. HRMS were determined with Agilent QTOF mass spectrometer

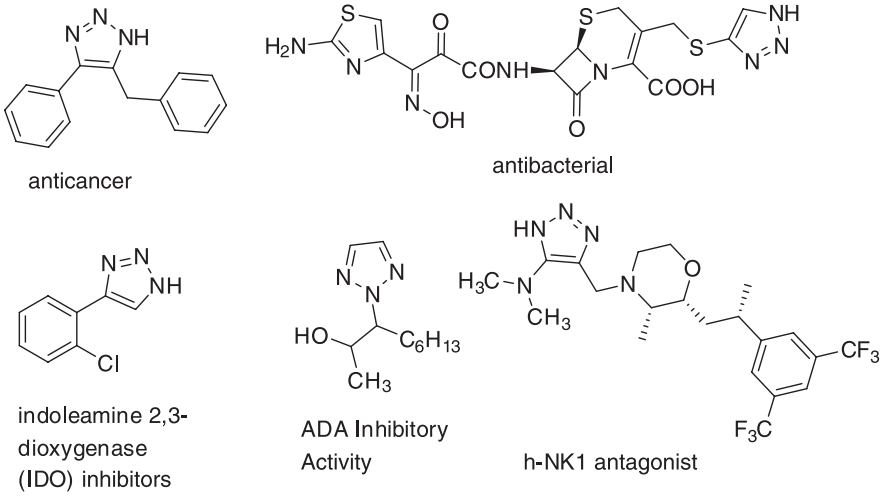


Figure 1. Representative structures of bioactive *NH*-1,2,3-triazoles.[13-17]

6540 series instrument. ESI-MS and ESI-MS/MS analyses were conducted in a Bruker Daltonics AmaZon SL ion trap mass spectrometer (Bruker Daltonics, Bremen, Germany). The ESI source and the mass spectrometer were operated in the negative ion mode, and the capillary voltage and drying gas temperature were –4.0 kV and 220 °C, respectively, with *m/z* scan range of 70-2000. Drying gas flow and nebulizing gas pressure were set to 5.0 L min^{-1} and 8.0 psi, respectively. MS/MS experiments were carried out by mass selection of a specific ion in ion-trap, which was then submitted to collision-induced dissociation (CID) with helium (He) in the collision chamber. Column chromatography was performed using silica gel of 60-120 and 100-200 μm with hexane and ethyl acetate as eluent.

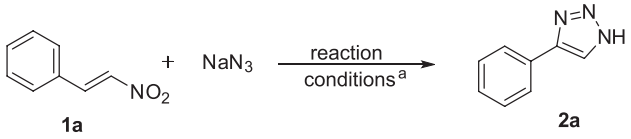
General procedure for the synthesis of compounds **2a-u**

Sulfamic acid (0.4 mmol) was added to a solution of nitroolefin **1a** (1.3 mmol) and sodium azide (2.0 mmol) in DMF (dimethylformamide). The reaction mixture was allowed to stir at 60 °C in air for the specified time. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with ice-water and extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford crude residue. The crude was purified by using column chromatography (SiO_2, EtOAc/hexanes) to afford the products **2a**. All the 4-aryl-*NH*-1,2,3-triazoles (**2a**-**u**) were prepared by the similar procedure (see electronic Supplementary Information (SI) section).

Results and Discussion

Initially, we carried out some of the model reactions with nitrostyrene (**1a**) and NaN_3 by using sulfamic acid in different solvents and reaction conditions to achieve the product 4-phenyl-*NH*-1,2,3-triazole (**2a**, Table 1). When the reaction was performed in the absence of sulfamic acid, the yields of **2a** were observed sluggishly even at 80 °C either by using DMSO or DMF as solvent (35, 28 and 40% yields, respectively, entries 1-3, Table 1) and the reaction led to the formation of considerable quantities of triarylbenzene.[15,20] To our delight, a significant increase in the yield was observed when sulfamic acid (0.2 equiv.) was used (69%, entry 4, Table 1) as additive in DMF at room temperature for 1 h. Later, we thought to optimize the reaction temperature and to increase the stoichiometric ratio of sulfamic acid (from 0.2 to 0.4 equiv.). It is interesting to observe that the reaction conversion and yields (80, 79, 85, 89 and 94%, respectively, entries 5-9, Table 1) were enhanced even with less reaction time. Next, we further increased the stoichiometric ratio of the sulfamic acid (up to 0.5 equiv.), but we did not observe any improvement in the yields (entry 10, Table 1).

Table 1. Optimization of the reaction conditions for the synthesis of **2a** from **1a**[a]



1a **2a**

entry	SA / equiv.	Solvent	time	Temperature / °C	Yield[b] / %
1	–	DMF	1 h	rt	35
2	–	DMSO	1 h	80	28
3	–	DMF	2 h	80	40
4	0.2	DMF	1 h	rt	69
5	0.2	DMF	30 min	60	80
6	0.2	DMSO	30 min	60	79
7	0.3	DMF	25 min	60	85
8	0.4	DMSO	20 min	60	89
9	0.4	DMF	20 min	60	94
10	0.5	DMF	20 min	60	92
11	1.0	MeOH	24 h	rt	50
12	1.0	MeOH	24 h	60	55
13	1.0	H_2O	30 min	60	< 5

[a]Reaction was carried out with **1a** (1.3 mmol), NaN_3 (2.0 mmol) and sulfamic acid (SA, indicated above equiv.); [b]isolated yields; DMSO: dimethylsulfoxide; DMF: dimethylformamide; rt: room temperature.

The reaction was also carried out in MeOH, however, optimal conversion was not observed (50 and 55%, and entries 11-12, Table 1). In the context of green chemistry point of view, we replaced organic solvent such as DMF with water and obtained only negligible yield (lower than 5%) (entry 13, Table 1). After optimization of the reaction conditions, finally the product **2a** was achieved in 94% yield by using sulfamic acid (0.4 equiv.) and DMF as suitable solvent at 60 °C for 15 min (entry 9, Table 1) without formation of any side product.

With optimized reaction conditions in our hand, then we explored the substrate scope of the protocol with various decorated nitroolefins to achieve different *NH*-1,2,3-triazoles (Table 2). Regardless of the substitution pattern, this protocol underwent 1,3-dipolar cycloaddition smoothly and accomplished the corresponding products in moderate to excellent yields (60-94% yields, **2a**-**u**, Table 2). Additionally, this methodology is highly compatible with a variety of functional groups, such as fluoro, chloro, bromo, methoxy, *o*-protected ethyl ester and *o*-protected *tert*-butyl ester, as shown in Table 2. It was our keen observation that all the cycloaddition reactions were completed in less than 1 h (10-45 min, Table 2). It is noteworthy that nitroolefins having with electron-donating groups *viz.* methoxy on the aryl ring resulted in the formation of products in excellent yield (87-91%, **2c**-**g**, Table 2). Much to our satisfaction, the optimized reaction conditions were mild enough to tolerate a range of halogenated (e.g., –F, –Cl, –Br) substrates with moderate to good yields (60-81%, **2h**-**j**, Table 2). In general, it could be easily deduced that the electronic properties of the substituent might have some effect on the formation of *NH*-1,2,3-triazoles as electron-releasing groups facilitated the formation of product in higher yields (87-91%, **2c**-**g**, Table 2) when compared to electron-withdrawing groups (60-81%, **2h**-**j**, Table 2). The substitution on aryl group at *ortho*-position to nitroolefin furnished the product in higher time as compared to other substrates (**2g** and **2k**, Table 2). Encouraged by these results, we turned our interest to heterocyclic substrates like furan and thiophene which are common motifs in medicinal chemistry. To our delight, the heterocyclic substituted nitroolefins proceeded smoothly in the cycloaddition reaction to provide their corresponding products **2l** and **2m** in good yields (80 and 85%, respectively, Table 2). Interestingly, the strongly coordinating heteroatoms like sulfur and oxygen have no interference to this reaction. Next, we moved on to explore the scope of this protocol with respect to di-substituted nitroolefins. It was quite interesting to note that the 1,3-dipolar cycloaddition reaction proceeded efficiently with di-substituted nitroolefins with high yield (92, 93 and 85%, respectively, **2n**-**p**, Table 2).

Furthermore, complex substrates like tricyclic nitroolefins were also investigated to explore the scope of this reaction. Gratifyingly, tricyclic substrate like phenanthrene nitroolefins underwent smooth cycloaddition and gave the corresponding products **2q** and **2r** in good yields (83 and 85%, respectively, Table 2). Similarly, nitroolefins having phenoxy alkyl ester *viz.* ethyl ester and *tert*-butyl ester efficiently participated and gave good yields (84 and 82%, respectively, **2s** and **2t**, Table 2) even without affecting the sensitive ethyl and tertiary butyl groups. However, the reaction performed with methyl nitroolefin gave a complex mixture of products under the same reaction conditions (**2u**). These results clearly indicated the scope and generality of sulfamic acid as additive or initiative for the synthesis of different 4-aryl-*NH*-1,2,3-triazoles by using a wide range of nitroolefins.

The functional nature of sulfamic acid could allow to activate β-nitrostyrene[24] through H-bonding (Figure 2) favoring the attack of azide to the molecule of nitrostyrene and leading to the formation of intermediate **3a**, which could immediately cyclise to form intermediate **4a** followed by loss of hydrogen and NO_2 to give final product **2a**. However, the addition of azide to nitrostyrene followed by conjugate addition to intermediate **3a** led to the formation of little quantities of nitroolefin dimer and the sodiated nitroolefin dimer of *m/z* 339. The formation of triphenylbenzene is a more complex process and is slower when compared to the formation of triazole.[15] Henceforth, activation of β-nitrostyrene by sulfamic acid could favor the immediate formation of triazole **2a** and could help in the reduction of byproduct formation.

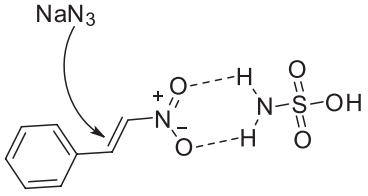
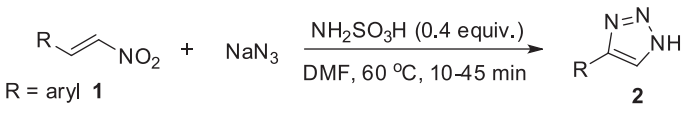


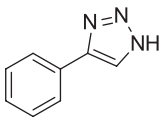
Figure 2. Possible transition state.

Although several mechanistic proposals are proposed for these transformations, we were intrigued by the fact that the action of an azide on nitrostyrenes did not afford the production of dimers/trimers in a great extension when employed H_3NSO_3. Thus, it is worthwhile to evaluate this transformation by on line ESI-MS studies. Electrospray ionization tandem mass spectrometry has been used by our group to study the mechanism of several catalyzed reactions by coupling on line microreactors to ESI-MS, and this combination showed significant advantages over more conventional parallel screening approaches.[25] ESI-MS experiments afford insight into the ionic reactive species

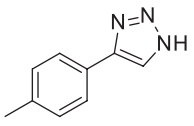
Table 2. Synthesis of substituted 4-aryl-*NH*-1,2,3-triazoles using NH_2SO_3H[a,b]



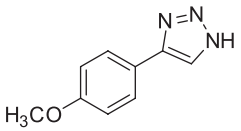
R = aryl **1** **2**



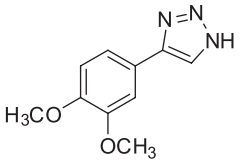
2a,94%[20]



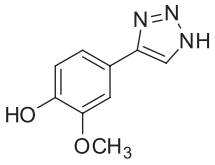
2b, 91%[20]



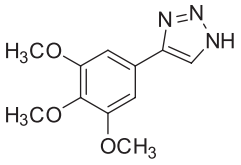
2c,87%[20]



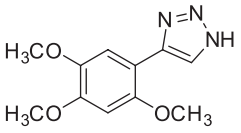
2d, 89%



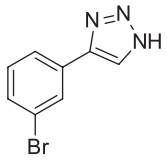
2e, 90%



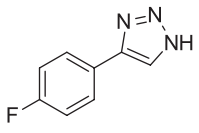
2f, 88%



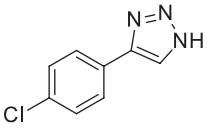
2g, 91%



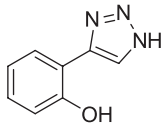
2h, 60%



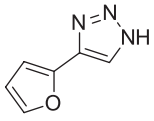
2i, 81%[20]



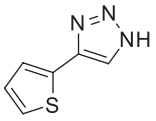
2j, 78%[20]



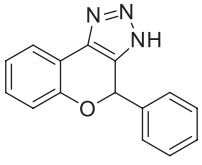
2k, 85%[20]



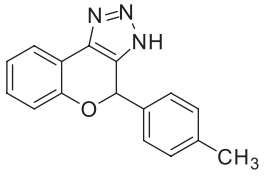
2l, 80%[20]



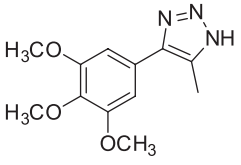
2m, 85%[20]



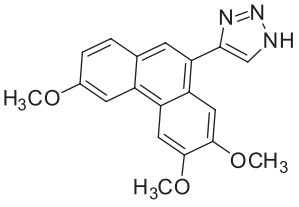
2n, 92%[20]



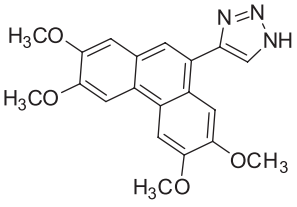
2o, 93%



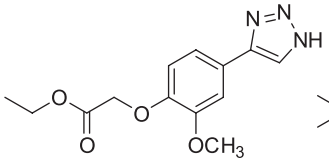
2p, 85%



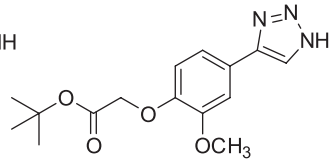
2q, 83%



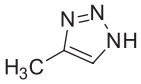
2r, 85%



2s, 84%



2t, 82%



2u, complex mixture

[a]Reaction conditions: nitroolefin (1.3 mmol), NaN_3 (2.0 mmol) and sulfamic acid (0.4 equiv.), dimethylformamide (DMF, 2 mL); [b]isolated yields.

taking a prominent role in organocatalytic reactions[26] since ESI can capture such ionic intermediates directly from solution to the gas phase for their unprecedented MS interception, mass identification and MS/MS structural characterization.[27] Based on our interest in the mechanistic study of organic reactions by mass spectrometry (MS),[28] which has greatly advanced from the development of electrospray ionization (ESI), we describe the experiments aimed to intercept the species produced from the on line monitoring of the sulfamic acid catalyzed reaction by using reactors coupled to ESI-MS. Although the proposed mechanism undergoes a 1,3-dipolar cycloaddition, the aim was to intercept the anionic species resulting from the proton-exchange equilibrium with NH_2SO_3H/DMF using ESI-MS in the negative ion mode. ESI is known for its ability to transfer ions to the gas phase without inducing undesirable side reactions, and the composition of ESI-generated ions often closely reflects that in solution.[25-27] The anionic reaction intermediates are likely to be in equilibrium with their respective neutral forms in solutions, and even disfavored equilibria could be useful because of the high sensitivity of ESI-MS analysis. Indeed, the ESI-MS spectra collected for such reactions are extraordinarily clean and mechanistically enlightening.

Initially, following our reaction protocol, sulfamic acid (0.4 mmol) was added to a DMF solution of nitroolefin **1a** (1.3 mmol) and NaN_3 (2.0 mmol). The reaction mixture was allowed to stir at 60 °C under an air atmosphere. Then, the solution was on line screened by using pressurized sample infusion (PSI) methodology,[29] which allows the monitoring of the reaction solution in real-time up to 8 h at 60 °C under stirring. Then, after 20 s to 1 min of reaction, three anionic species can be observed (Figure 3), which are detected as major ions (Figure 3a), *m/z* of 297, 339 and 361. The main ion of *m/z* 297 was characterized by ESI(–)-MS/MS and afforded a characteristic fragmentation pathway that showed main losses of $[M–HCOH]^-$ (*m/z* 267), $[M–HCOH–PhH]^-$ of (*m/z* 219) and $[M–DMF–SO_3]^-$ (*m/z* 144). This species can be seemed as a stabilized triazole species that is observed in the catalyzed sulfamic acid

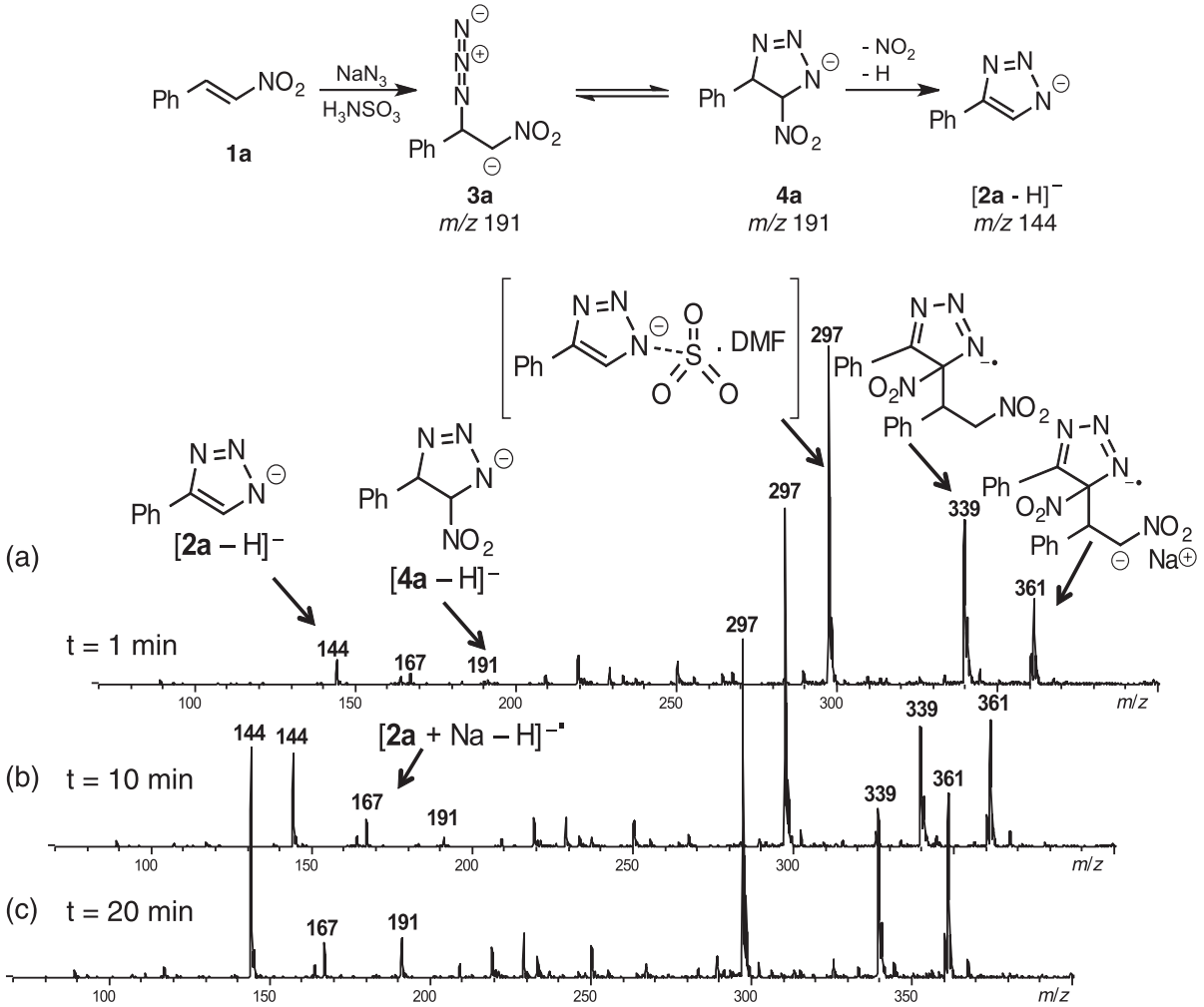


Figure 3. On line ESI(–)-MS screening of the reaction of **1a** and NaN_3 using H_3NSO_3 in DMF to produce *NH*-1,2,3-trizole **2a**.

Table 3. Different reaction for the synthesis of 4-aryl-*NH*-1,2,3-triazoles

entry	Reaction	Catalyst	Solvent	time	Temperature / °C	Yield[a] / %
1	**1a** + NaN_3	–	DMSO	–	rt	60 + triarylbenzene[15]
2	phenylacetylene + $TMSN_3$ (*in situ* HN_3)	Cu^I (20 mol%)	MeOH/DMF	11 h	100	87[18]
3	**1a** + NaN_3	*p*-TsOH (0.5 equiv)	DMF	1 h	60	93[20]
4[b]	**1a** + NaN_3	sulfamic acid (0.4 equiv)	DMF	20 min	60	94

[a]Isolated yields; [b]present work; DMSO: dimethylsulfoxide; DMF: dimethylformamide; rt: room temperature.

reaction. The other two species of *m/z* 339 and 361 were characterized as the nitroolefin dimer and the so sodiated nitroolefin dimer, respectively, which were produced in the first stages of reactions as depicted in Figure 3a. Furthermore, small amounts of anionic [**4a**–H]$^-$ of *m/z* 191 and [**1a**–H]$^-$ of *m/z* 144 were also observed at 1 min reaction time. Between 10 to 20 min of reaction, the species [**1a**–H]$^-$ increases (Figures 3b-3c), which is the final product obtained from the nitration of [**4a**–H]$^-$ in solution. The characterization of the species [**4a**–H]$^-$ was performed by ESI-MS/MS experiments, which afforded as expected, one main fragment pathway producing intermediate [**1a**–H]$^-$ by losses of H and NO_2, respectively.

The experiments were carried out in negative ion mode (*m/z* range of 70-600). The samples were on line infused into the ESI source, via a pressurized reactor, at flow rates of 10 μL min^{-1}. After mixing the reagents at 60 °C in a DMF solution and ESI(–)-MS analysis after 1 min, a small amount of intermediate **4a** (*m/z* 191) was observed (Figure 3). It is worth to note that between 1-20 min reaction time, the presence of the species of *m/z* 297 was observed being characterized as **2a**.SO_3-DMF complex. The presence of this complex might prevent the production of undesired dimers-trimers in the reaction, affording higher yields of **2a**, which justified theuse of H_3NSO_3 in this class of reactions.

In order to show the merit of this methodology, the synthesis of 4-aryl-*NH*-1,2,3-triazoles in the presence of sulfamic acid was compared with some of the previous methods as shown in Table 3. As it is obvious from the results, the reaction in the absence of catalyst led to the formation of considerable quantities of triarylbenzene,[15] however the reaction of phenylacetylene required more time for completion.[20] Furthermore, the reaction of nitrostyrene **1a** with sodium azide in the presence of sulfamic acid completed in less time as compared to *p*-TsOH[20] being the advantage of this method compared to the previous ones.

Conclusions

In conclusion, we have developed a facile and reproducible 1,3-dipolar cycloaddition reaction from nitroolefins by employing sulfamic acid as additive towards the synthesis of a valuable substituted 4-aryl-*NH*-1,2,3-triazoles. This method proved to be a possible alternative to the classical Huisgen 1,3-dipolar cycloaddition of azides with alkynes. Easily available starting materials, simple process, inexpensive reagents and open to air are the salient features of this protocol. In addition, the key intermediates related to this reaction mechanism were proposed by online monitoring through ESI-MS/MS experiments. This methodology is practically applicable for all kind of nitroolefins and displayed great functional group compatibility. More importantly, this strategy enables rapid validation of library synthesis of 1*H*-1,2,3-triazoles as new chemical entities in the drug discovery.

Supplementary Information

Spectroscopic data and ^1H and ^{13}C NMR spectra for **2a**-**2t** are available free of charge at http://jbcs.sbq.org.br as PDF file.

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