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Rapid and efficient synthesis of formamidines in a catalyst-free and solvent-free system†

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An operationally rapid and efficient synthesis of *N*-sulfonyl formamidines that proceeds under mild conditions was achieved by reaction of a mixture of an amine, a sulfonyl azide, and a terminal ynone under catalyst-free and solvent-free conditions. Terminal ynones provide the C source to formamidines via complete cleavage of C≡C.

Amidines are ubiquitous in nature and have critical roles in pharmaceutical and agrochemical industries.¹ In addition, amidine derivatives have been documented as key scaffolds in drug discovery² and crucial fragments in numerous biologically relevant molecules.³ As a unique class of amidines, *N*-sulfonyl formamidines are widespread in insecticidal/acaricidal drugs⁴ or biologically active molecules.⁵ As shown in Fig. 1, acaricidal drugs include ebrotidine (a),⁶ inhibitors of steroid sulfatase (b),⁷ antagonists/inverse agonists (c)⁸ and antimicrobial agents (d).⁹ Therefore, development of novel, efficient and sustainable methods for the synthesis of *N*-sulfonyl formamidines has been a consistent focus of synthetic chemists.

Four main synthetic methods for preparation of *N*-sulfonyl formamidines have been reported. The first is the condensation of sulfonamides with formamides using an oxidant to generate a reactive electrophilic intermediate (Scheme 1a).¹⁰ The second method is the reaction of sulfonamides with amines involving oxidation of the amine to an iminium cation generated electrochemically^{11,12} or by reaction of Cu(II) (generated *in situ* by aerial oxidation of CuBr at 100 °C) (Scheme 1b).¹³ The third method is cycloaddition of a sulfonyl azide to an enamine intermediate generated by oxidation of a trialkylamine followed by retrocycloaddition to generate a diazoalkane concomitantly (Scheme 1c).^{14–16} The fourth method is a three-component reaction, reported previously by our research team, between a sulfonyl azide, a terminal ynone (3-butyne-2-one) and an amide involving the formation of a highly reactive intermediate *N*-

sulfonyl acetylketenimine reacting with the amide in a [2 + 2] cycloaddition followed by a [2 + 2] cycloreversion with the concomitant generation of 4-oxo-3-buten-2-one (Scheme 1d).¹⁷ Recently, Wusiman and colleagues proposed a straightforward one-pot multicomponent approach, but heating and solvent addition are required.¹⁸ Each of the methods described above has considerable advantages, including mild reaction conditions and high efficiency in the assembly of *N*-sulfonyl formamidines. However, their synthetic utility is impaired by the requirement of environmentally unfriendly solvents, metal catalysts and/or relatively long reaction times or high temperatures.

Scheme 1 reveals an operationally simple protocol involving stirring a mixture of an amine, a sulfonyl azide, and a terminal ynone without a catalyst or solvent.

Our investigations began with examination of the synthesis of the parent and previously unreported system 4-methyl-*N*-(morpholinomethylene)benzenesulfonamide **4aa** via morpholine **1a**, *p*-tosyl azide **2a** and but-3-yn-2-one **3a**. We first detected this unconventional product **4aa** in a CuAAC/ring-opening reaction system with a low yield (8%, Table 1, entry 1). After screening using AgTFA/MeCN as a catalyst condition, product **4aa** was obtained in high yield of 90% (Table 1, entry 2). If AgTFA or MeCN were not added, the yield of the product decreased (Table 1, entries 3 and 4). To our delight, the reaction

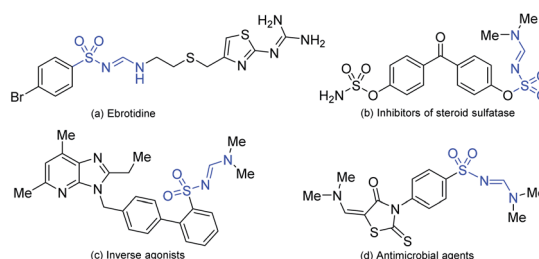


Fig. 1 Some formamidines drugs or drug candidates.

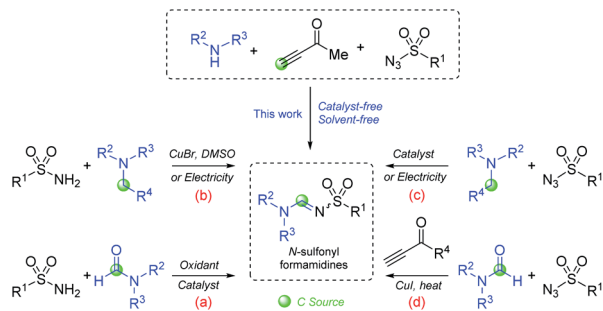
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Scheme 1 Synthesis of *N*-sulfonylformamidines.

delivering product **4aa** in highest yield was catalyst-free under a neat condition in 2 min (95%, Table 1, entry 5). Curiously, compound **4aa** did not contain all the fragments of but-3-yn-2-one **3a**. Therefore, different terminal alkynes were detected. Additional screening revealed that the terminal ynones **3b–3d** gave comparable yields (Table 1, entries 6–8). For example, ethyl propiolate **3b** gave a yield of 90% in 3 min and *tert*-butyl propiolate **3c** gave a yield of 92% in 5 min. Phenylacetylene **3d** was used, but it failed to produce the desired product (Table 1, entry 9). Considering atomic economy, speed and efficiency, the “parent reaction” was defined to the condition of Table 1, entry 5.

Under the optimized conditions, the capacity of this reaction to affect the coupling of a range of different substrates was investigated. As revealed in Table 2, various structurally and electronically distinct amines engaged readily in the desired reaction to give the anticipated products (**4aa–4ax**) in modest-to-good yields. Secondary amines of alkyl groups proved more effective substrates than their aromatic counterparts (**4aa–4ae**,

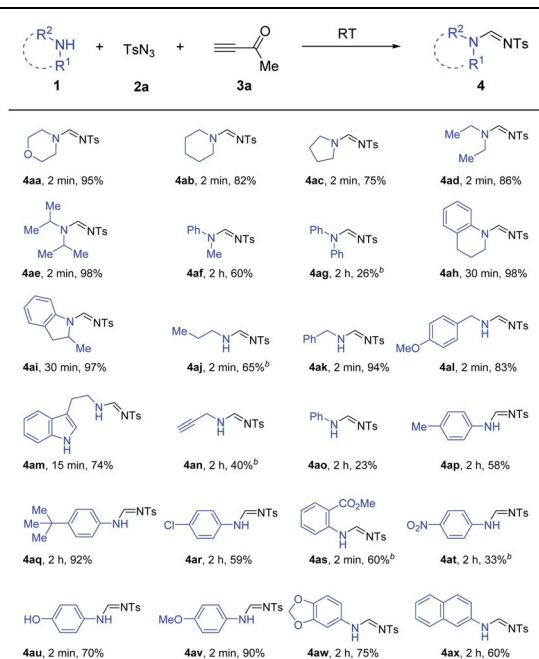
75–98% yield vs. **4af–4am**, 26–98% yield) with the best “performing” member of the latter group being 1,2,3,4-tetrahydroquinoline and affording the anticipated product **4ah**. Likewise, the structure of primary amines could be varied to a reasonable degree to elicit products (**4aj–4ax**), but showed lower efficiency than that of secondary amines. Most aliphatic primary amines elicited modest yields whereas the substrate benzylamine gave the products **4ak** in high yield of 94%. Electron-withdrawing and electron-donating groups attached to the aromatic ring of aromatic primary amines of the general form **4** (e.g., methyl, halogen, ester, 2-naphthyl and nitro) were tolerated, as evidenced by formation of the anticipated products, **4ao–4ax**, in serviceable yield. However, amines derived from tertiary amines, heterocyclic and inorganic ammonium salts failed to transfer into the corresponding products under the optimized conditions.

Next, the scope and limitation of substrates sulfonyl azides **2** were tested. Importantly, the substrates sulfonyl azides showed rapidity and efficiency in this reaction. Change of R^3 by aromatic or aliphatic substituents, such as phenyl, $-(4\text{-CF}_3\text{C}_6\text{H}_4)$, $-(4\text{-NO}_2\text{C}_6\text{H}_4)$, $-(4\text{-OMeC}_6\text{H}_4)$, $-\text{Me}$, ^{-t}Bu or benzyl, enabled the reaction to run smoothly to give the anticipated products (**4ba–4bl**) in good yields of 88–96%. All products were produced mainly in the *E*-*syn* conformation (for details please see the spectra in the ESI†) (Table 3).

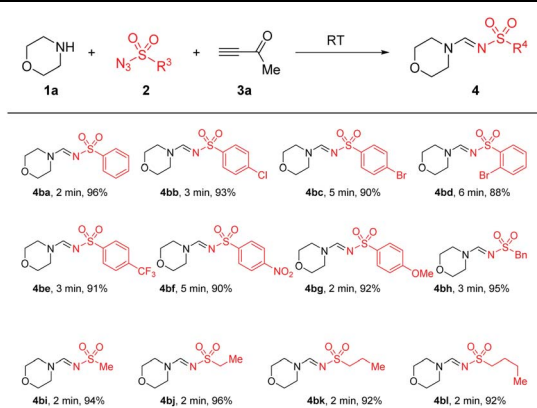
Table 1 Optimization of conditions^a

Entry	Alkyne 3	Cat./solvent	Time	Yield ^b (%) 4aa
1	3a	CuI/MeCN	4 h	8
2	3a	AgTFA/MeCN	4 h	90
3	3a	—/MeCN	12 h	79
4	3a	AgTFA/—	1 min	56
5	3a	—/—	2 min	95
6	3b	—/—	3 min	90
7	3c	—/—	5 min	92
8	3d	—/—	6 min	70
9	3e	—/—	12 h	0

^a Reaction conditions: **1a** (0.1 mmol), Cat. (2.0 mol%) in the solvent (3 mL) was added slowly to **2a** (1.8 equiv.) and **3** (1.8 equiv.) in order, then stirred at room temperature for the corresponding time (detected by TLC or solidification). ^b Isolated yields.

Table 2 Substrate scope of amines **1**^a

^a Reaction conditions: **1** (0.1 mmol) and **2a** (1.8 equiv.) were added, then **3a** (1.8 equiv.) was added slowly, and stirred at room temperature for the corresponding time (detected by TLC or solidification). ^b Reaction conditions: **1** (0.1 mmol) and AgTFA (2 mol%) in MeCN (3 mL) was added to **2a** (1.8 equiv.) and **3a** (1.8 equiv.), then stirred at 60 °C for the corresponding time (detected by TLC).

Table 3 Substrate scope of the sulfonyl azides 2^a

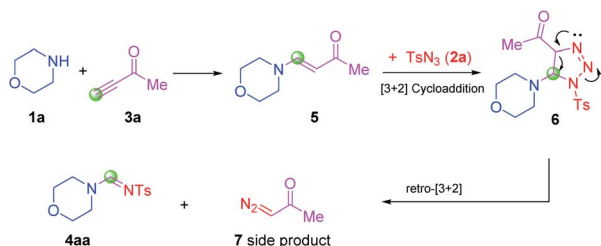
^a Reaction conditions: **1a** (0.1 mmol) and **2** (1.8 equiv.) were added, then **3a** (1.8 equiv.) was added slowly, and stirred at room temperature for the corresponding time (detected by TLC or solidification).



Scheme 2 Investigation of the reaction mechanism.

According to recent reports of complete cleavage of $C\equiv C$ ¹⁹ and the reaction characteristics of ynone,²⁰ further experiments were carried out to gain deeper understanding of the mechanistic pathway (Scheme 2). We undertook the reaction of **2a** with 4-morpholinobut-3-en-2-one **5**, which was synthesized by **1a** and **3a**, under the standard conditions. The corresponding products **4aa** were generated with a yield of 75%. The desired product could not be obtained without terminal ynone. Taken together, these results implied that the terminal ynone provided the C source to formamidines *via* complete cleavage of $C\equiv C$, and that compound **5** might be an intermediate.

Based on the results stated above and related precedent,^{19,21} a plausible mechanism for the formation of *N*-sulfonyl formamidines (**4aa**) from precursors **1a**, **2a** and **3a** is shown in Scheme 3. First, the substrates **1a** and **3a** are expected to take Michael addition to form the intermediate 4-morpholinobut-3-en-2-one **5**. This species is captured by tosyl azide **2a** by participating in the [3 + 2] cycloadditions to generate the 1,2,3-



Scheme 3 Plausible reaction mechanism.

triazoline intermediate **6**, which itself undergoes retro-[3 + 2]-cycloaddition to yield the product **4aa**, with elimination of the side-product 1-diazopropan-2-one **7**.²¹

Conclusions

We developed an operationally rapid and efficient reaction for preparing *N*-sulfonyl formamidines from a mixture of mines, sulfonyl azides and terminal ynone with catalyst-free, solvent-free, mild conditions and a wide scope of substrates. From a mechanistic perspective, the terminal ynone has a critical role in cleavage, and provide the C source to formamidines *via* complete cleavage of $C\equiv C$. This methodology appears quite flexible and can generate forms of the title products that will be particularly useful in, for example, drug-development studies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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