Journal of Scientific Research
Banaras Hindu University, Varanasi

Vol. 63, 2019 :185-190
ISSN : 0447-9483

EXPLORATION OF SYNTHETIC PROPERTIES OF SULFONIMIDAMIDES

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Abstract:

During the last one and half decade, chemists within widely different areas of science have observed a rising attentiveness in chemical matters incorporating the sulfonimidamide functional group. New synthetic routes to sulfonimidamides have been reported, and the utility of these products have been established in synthetic, agrochemical, medicinal,, and material science applications.* In this mini report, the research work that has been performed by our group on this moiety have been discussed.

Keywords: Sulfonimidamides; N-functionalization, Sulfonimidoyl azides, Multicomponent reactions

Introduction

Sulfonimidamides **2** (SIAs), the mono aza-analogues of sulfonamides (SAs) **1**, in which one of the sulfonamide O-atom has been replaced by a *N*-atom, were first published by Levchenko et al. in the early 1960's.[1] The replacement of one oxygen atom of a sulfonamide **1** with a nitrogen atom not only provides a novel class of compound – a sulfonimidamide, but also creates a new stereogenic sulfur center and delivers the possibility of introducing extra structural diversity (i.e., substituent R^5) around the broadly used sulfonamide functional group (Figure **1**). Fascinatingly, when the amide handle (sp^3 hybridized) is primary or secondary, the SIA undergoes tautomerism due to exchange of proton between amide and imide group. The relative stability of the tautomer depends upon the nature of substituents present in R^5 and R^6. Both the theoretical and experimental studies revealed that the tautomer **2'** is more stable than tautomer **2'** when the imine (sp^2 hybridized) nitrogen atom is attached with a group that allows conjugation, e.g., an "acyl" protecting group i.e. R^5 = COR). The use of an "acyl" protecting groups has practical consequences, as it often simplifies synthetic transformations and product analysis. The tautomeric nature of the SIAs exhibit interesting property that is imino nitrogen may act as both a hydrogen bond donor and acceptor depending on the protonation state.

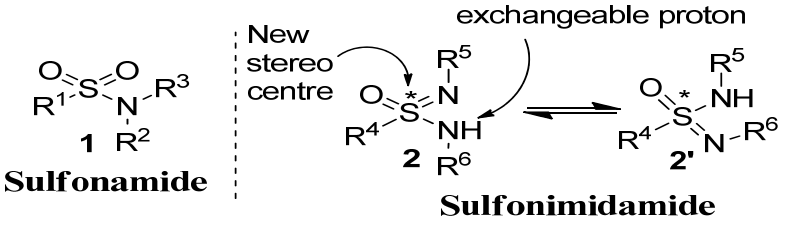
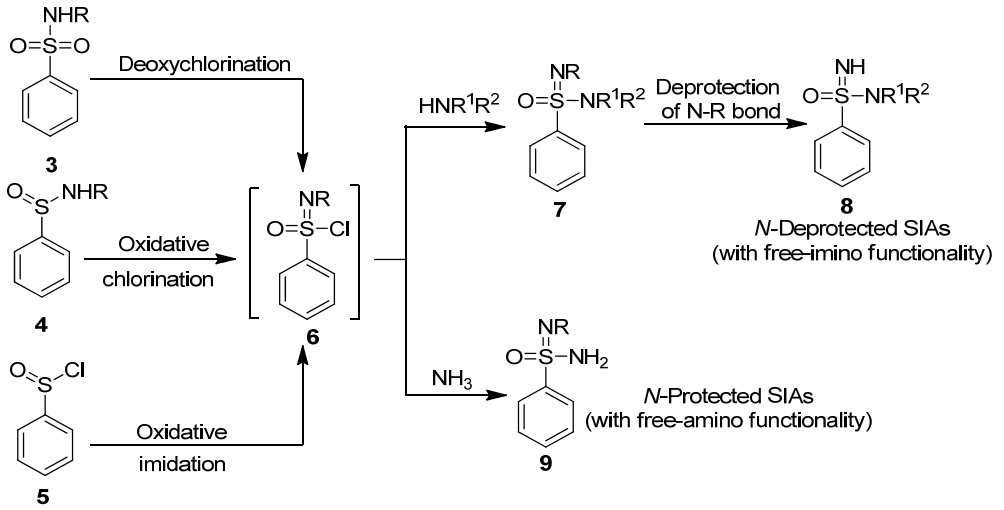


Figure 1. Structure of sulfonamide and sulfonimidamide.

Since the pioneering work on the synthesis of SIAs in the 1960s, the chemistry and applications of these hexavalent stereogenic sulfur moities were long been overshadowed. However, during the last two decades, there has been an increased attention in this functional group in the areas of synthetic- and biological chemistry, as well as material science. Consequently, a number of articles and patents have been published and an increasing amount of research is being reported around this moiety. In light of this renewed interest, Arvidsson *et. al.* reviewed the use of SIA containing substances for medicinal- and agrochemical applications.[2]Another review covers mainly the synthetic utilizations SIAs.[3] However, in this mini report, the research work that has been performed by our group on this moiety will be discussed.

Synthesis of Sulfonimidamides

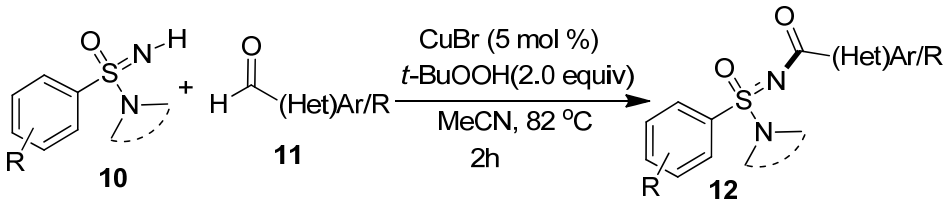
Levchenko *et al.* described the first report on the synthesis of SIAs in 1960.[1] The synthetic route needed the formation of an intermediate sulfonimidoyl chloride **6**, which upon nucleophilic substitution with an amine afforded the SIAs **7**. Scheme **1** demonstrated the different routes towards the synthesis of sulfonimidoyl chlorides **6**. The procedure include direct transformation of sulfinyl chloride **5** into sulfonimidoyl chloride **6** *via* oxidative imidation using various *N*-chloro compounds, such as chloramin T, dichloramin T, *N*,*N*-dichloromethylamine, and the sodium salts of *N*-chloroamides. Sulfinamides **4** may also yield sulfonimidoyl chlorides **6** *via* oxidative chlorination employing chlorinating agents like chlorine, anhydrous chloramines T, *N*-chlorobenzotriazole, *t*-butylhypochloride, and *N*-chlorosuccinimide (NCS).[4] A direct conversion of readily available mono *N*-substituted sulfonamides **3** into the sulfonimidoyl chlorides **6** *via* deoxychlorination exploiting PCl_5 as chlorinating agent was also reported by Levchenko *et al.* Later, in 1993, Roy utilized a new chlorinating agent triphenyldichlorophosphorane- (Ph_3PCl_2),[5] which showed better activity than PCl_5. In 2015, Chen and Gibson applied Roy's reagent for a one-pot procedure of converting silyl protected SAs to SIAs.[6] A comprehensive accounts for the synthesis of sulfonimidoyl chloride **6** has been described in a review by Levchenko et al.[7]



Scheme-1. Method and reagents for the synthesis of sulfonimidoyl chlorides and SIAs.

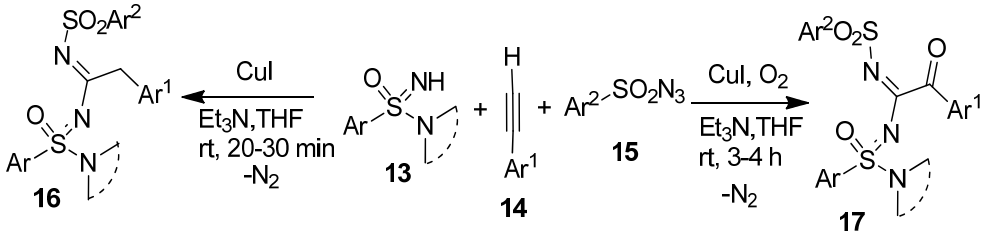
Synthetic Exploration

In 2017, A novel method for the synthesis of *N*-acyl SIAs **12,** *via* a Cu-catalyzed double C-H/N-H activation process, has been disclosed (Scheme **2**).[8] The imino end of SIAs **10** was acylated utilizing aldehyde **9** as an acylating agent, *t*-butyl hydrogen peroxide (TBHP) as an oxidant in acetonitrile (MeCN) at 82 °C. The mild reaction conditions afforded low to moderate yields of *N*-acyl SIAs **10** with awide structural diversity.



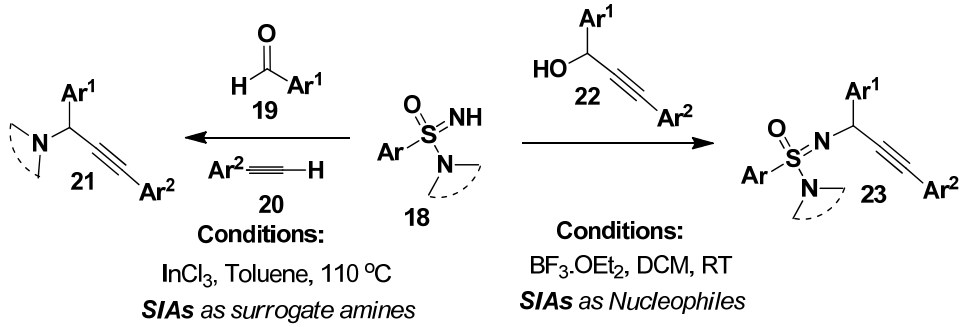
Scheme-2. N-Acylation of SIAs through Cu-catalyzed C-H/N-H dual activation.

In another recent report, we synthesized *N*-imidoyl SIAs **16** through a mild Cu-catalyzed one-pot three-component reaction of SIAs **13**, alkynes **14** and azides **15** in THF at room temperature under air in moderate to good yield (Scheme **3**).[9] In addition, in the presence of molecular oxygen, the *N*-imidoyl SIAs **16** were further oxidized to provide *N*-oxoimidoyl SIAs **17**. It is the first report where SIAs have been utilized in the multi-component reactions for the first time.



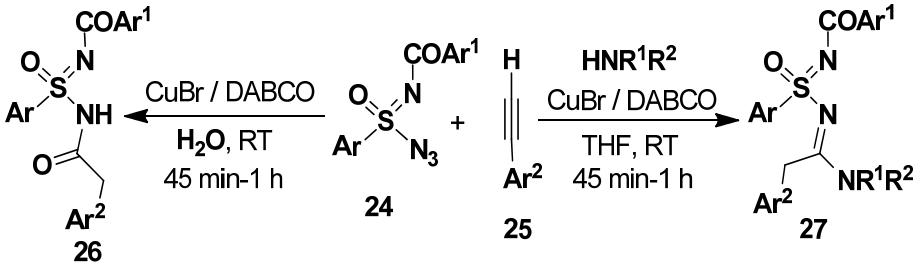
Scheme-3. N- Imidoylation/oxoimidoylation of SIAs via Cu- catalyzed three component coupling.

In an another current report, an unfamiliar characteristic of SIAs have been discovered. The SIAs **18** were reacting as surrogate amines in a metal ($InCl_3$)-catalyzed multi-component A^3 coupling reaction with aldehydes **19** and acetylenes **20** to afford propargylamines **21** in very good to excellent yield (Scheme **4**).[10] Furthermore, a new protocol describing the nucleophilic behavior of SIAs **18** to access *N*-propargyl SIAs **23** *via* the direct-imination of propargyl alcohols in the presence of $BF_3.OEt_2$ has also been described.



Scheme-4. Catalyst-controlled dual reactivity of SIAs: as surrogate amines and as nucleophiles.

Sulfonimidoyl azides **24**, the novel aza-analogue of sulfonyl chloride, has been designed, synthesized and utilized for the construction of *N*-Acyl sulfonimidamides **26** and *N*-sulfonimidoyl amidines **27**. *N*-Acyl sulfonimidamides **26** were synthesized in good to very good yields *via* "on water" copper-catalyzed three component coupling of sulfonimidoyl azide **24**, alkynes **25** and water.[11] The use of amines instead of water as nucleophiles yielded a wide range of *N*-sulfonimidoyl amidines **27**(Scheme **5**). Both reactions were completed in very short time at room temperature under mild conditions, thus establishing the potential of sulfonimidoyl azides **24**, the chiral aza-analogues of sulfonyl azides, as an excellent precursor to derive functionalized sulfonimidamides in one step.



Scheme-5. Sulfonimidoyl azides as novel precursors to access N- acyl SIAs and sulfonimidoyl amidines.

Conclusions

In this mini report, all reported synthetic protocols to SIAs and their synthetic applications that has been performed in our laboratory have been summarized (till date). As recently reviewed, SIA containing compounds are initiating to become utilized as a design scaffold in molecules with biological importance.[2] In the laboratory, we mainly focused on the new aspects as well as new synthetic routes to SIAs.

In spite of the exploration of this functional moiety has been surprisingly late and slow, the scaffold is now continuously receiving a growing interest in different aspects of molecular science. The main constraint for exploring SIAs applicability can be attributed to a lack of simple synthetic routes for their preparation, but a few recent reports has adequately addressed this issue (too on large scale) through novel methods to the functional group. What remains to be improved are more efficient asymmetric syntheses (catalytic) of chiral SIA derivatives.

There are also limited reports on the basic chemical properties of the SIA functional group to make general conclusions, but the complexity, opportunities for diversity, and fascinating properties arising due to the difference in reactivity of amino and imino handle as well as the stereogenic sulfur centre, and their tautomers offers plenty of opportunities for such explorations *via* theoretical and experimental studies!

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