Review Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

Recent progress in the direct sulfonylation of C(*sp*)-H/CO_2H bonds

I.B. Sapaev[1,2,3,*], Makhmudova Nilufarkhon[4], Khudayberdiyev Oribjon[5], Kobilov Aziz[6], Javlonbek Madaminov[7], Nilufar Esanmuradova[8,9,10], Abdullayev Dadaxon[11], Alisher Ishankulov[12,13], Malokhat Jumaeva[14], Mukhlisa Rustamova[7], Abdurasul Kholmurzayev[7], Isayev Fakhriddin[15], Akhmadov Inomjon[16]

[1]*Department of Physics and Chemistry, Tashkent Institute of Irrigation and Agricultural Mechanization Engineers, National Research University, Tashkent, Uzbekistan.*
[2]*University of Tashkent for Applied Science, Tashkent, Uzbekistan.*
[3]*Western Caspian University, Scientific researcher, Baku, Azerbaijan.*
[4]*Literature Department of English Language and Literature, Faculty of English Language and, Andijan State Institute of Foreign Languages, Andijan, Uzbekistan.*
[5]*Department of Mechanical Engineering Technology, Faculty of Mechanical Engineering Technology, Andijan State Technical Institute, Andijan, Uzbekistan.*
[6]*Department of Biotechnology and Food Safety, Bukhara State University, Bukhara, Uzbekistan.*
[7]*Department of Architecture and Computer Graphics, Faculty of Architecture and Construction, , Fergana State Technical University, Fergana, Uzbekistan.*
[8]*Tashkent Institute of Irrigation and Agricultural Mechanization Engineers, National Research University, Tashkent, Uzbekistan.*
[9]*School of Engineering, Central Asian University, Tashkent, 111221, Uzbekistan.*
[10]*Baku Eurasian University, Baku, AZ 1073, Azerbaijan.*
[11]*Department of Fruits and Vegetable Growing, Urgench State University, Urgench, Uzbekistan.*
[12]*Samarkand State University, Samarkand, Uzbekistan.*
[13]*Kimyo International University in Tashkent, Samarkand, Uzbekistan.*
[14]*Department of Nuclear Medicine and Medical Radiology, Bukhara State Medical Institute, Bukhara, Uzbekistan.*
[15]*Scientific Research Center of Scientific Foundations and Problems of the Development of the Economy of Uzbekistan, Tashkent State University of Economics, Tashkent, Uzbekistan.*
[16]*Department of Dentistry, Faculty of Postgraduate Education, Samarkand State Medical University, Samarkand, Uzbekistan.*

ARTICLE INFO

Article history:
Received 17 August 2025
Received in revised form 11 September 2025
Accepted 13 September 2025
Available online 18 October 2025

Keywords:
Decarboxylative functionalization
C-H bond functionalization
Sulfonylation
Acetylenes
Acetylenic acids
Acetylenic sulfones

ABSTRACT

The direct sulfonylation of terminal acetylenes and the decarboxylative sulfonylation of acetylenic acids are novel and straightforward approaches for preparing biologically and synthetically significant acetylenic sulfone derivatives. These methods offer several advantages over conventional protocols, including the utilization of inexpensive and readily accessible starting materials, improved atom and step economy, and reduced waste generation. This mini-review highlights recent advancements in these promising approaches to acetylenic sulfones, with an emphasis on the scopes, limitations and the mechanisms of the reactions.

1. Introduction

Sulfones constitute a privileged class of organosulfur compounds with numerous applications in various fields ranging from pharmaceuticals [1] and agrochemicals [2] to functional materials (dyes, pigments, plastics, polymers, etc.) [3]. Acetylenic sulfones are one of the most important family of this class of compounds that display a broad spectrum of biological activities [4]. Furthermore, owing to their diverse reactivity, they have extensively utilized as key building blocks in the assembly of various biologically significant cyclic and acyclic compounds, including as α-ketothioesters, quinolones, 1,2,3-triazoles, isoquinolones, and internal alkynes, among others [5-7]. Additionally, they have widely utilized as efficient starting materials in the construction of a diverse range of natural products such as (-)-(*ent*)-julifloridine, (-)-pumiliotoxin C, (-)-lasubine

* Corresponding author E-mail: sapaevibrokhim@gmail.com
https://doi.org/10.22034/crl.2025.541787.1678

II and (±)-myrtine [8]. These facts underscore the privileged status of organosulfur frameworks, whose presence critically governs electronic behavior and functional performance in biologically and technologically relevant molecules [9-13].

Considering the extensive synthetic applications and biological activities of the titled compounds, their synthesis has attracted considerable attention over time [14]. Conventional methods for the synthesis of acetylenic sulfones can be classified into six main categories: (i) oxidation of alkynyl sulfides [15]; (ii) elimination of selenovinyl sulfones [16]; (iii) dehydrohalogenation of halo vinyl sulfones [17]; (iv) sulfonylation of 1-haloalkynes [18]; (v) sulfonylation of alkynyl lithium [19]; and (vi) sulfonylation of aryl alkynyl iodonium salts [20]. While these protocols offer certain advantages, they also have notable drawbacks, including the requirement for pre-functionalized starting materials, the generation of unwanted by-products, and the use of harsh reaction conditions, among others. To address these limitations, the direct sulfonylation of abundantly available terminal acetylenes and decarboxylative sulfonylation of readily accessible acetylenic acids have recently emerged as appealing alternatives to traditional $C_{(alkynyl)}$-SO_2R forming reactions that offer several advantages over the conventional methods such as the use of nontoxic, inexpensive, and simple starting materials, as well as high atom- and step-economy, and the minimization of waste generation. This mini-review provides an overview of these rapidly growing areas, with a particular focus on the scope, limitations, and mechanisms of the reactions (Figure 1). Literature has been surveyed until the end of 2024.

2. Direct sulfonylation of terminal acetylenes

In this section, we describe the current literature on the direct sulfonylation of terminal acetylenes using different sulfonylation agents. The section is divided into four subsections according to the type of sulfonylating agents: $C_{(alkynyl)}$–H sulfonylation reactions using (i) sulfinic acids as sulfonylation agents; (ii) sulfonyl hydrazides as sulfonylation agents; (iii) sodium sulfinates as sulfonylation agents; and (iv) thiosulfonates as sulfonylation agents.

2.1. Sulfinic acids as sulfonylation agents

The first and only example of the direct C-H sulfonylation of terminal alkynes employing sulfinic acids as sulfonylation agents was described by Wang and co-workers in 2015 [21].

They showed that treatment of phenylacetylene 1 with benzenesulfinic acid 2 in the presence of 1 equiv. of molecular iodine (I_2) as an iodination reagent and 2 equiv. of K_2CO_3 as a base in DMF at 100 °C, resulted in ((phenylethynyl)sulfonyl)benzene 3 in 78% yield within 12 h (Scheme 1). Notably, when the reaction was performed in the absence of a base, the corresponding (*E*)-β-iodovinyl sulfone was obtained as the sole product. Although only a single example was presented, as noted above, this paper represents the first instance of the direct C(*sp*)-H sulfonylation using sulfinic acids and could serve as an inspiration for further researchers.

2.2. Sulfonyl hydrazides as sulfonylation agents

In 2019, Huang and Tang along with their co-workers developed an efficient oxidant-free electrochemical oxidative cross-coupling reaction between terminal (hetero)aromatic alkynes 4 and (hetero)aryl sulfonylhydrazides 5 for the synthesis of acetylenic sulfones 6 [22]. In an undivided cell assembled with a reticulated vitreous carbon (RVC) anode and platinum plate cathode, the best reaction conditions were achieved with tetrabutylammonium iodide ($^nBu_4NI$) as the electrolyte and redox medium, K_2CO_3 as a base, and aqueous acetonitrile as the solvent, with a constant potential of 1.2 V vs. Ag/AgCl under the oxygen atmosphere (Scheme 2). Interestingly, aromatic alkynes having either electron-donating (*e.g.*, Me, ^{t}Bu) or electron-withdrawing (*e.g.*, CF_3, CO_2Me) substituents were compatible with this synthetic strategy. In addition, the scope of sulfonylhydrazides that underwent reaction was broad enough to include aryl, heteroaryl, and naphthyl sulfonylhydrazides. However, neither aliphatic alkynes nor aliphatic sulfonylhydrazides were reacted under the conditions employed. The authors suggested mechanism to explain this cross-coupling reaction is depicted in Scheme 3.

In this study, the authors also investigated the synthetic application of prepared acetylenic sulfones as intermediates and achieved various useful compounds such as internal alkynes, alkynyl alkyl ethers, alkynyl-(diaryl)phosphine oxides, β-keto sulfones, and triazoles in moderate to excellent yields. The authors further investigated the biological activities of the synthesized acetylenic sulfones by assessing their *in vitro* antitumor effects through MTT assays on the MGC-803, HepG2, T-24, HL-7402, and HeLa tumor cell lines. Intriguingly, most of the compounds exhibited strong inhibitory activity against the tested tumor cell lines.

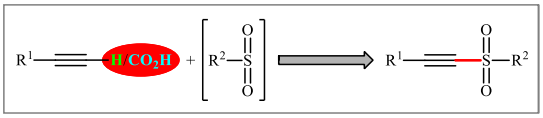
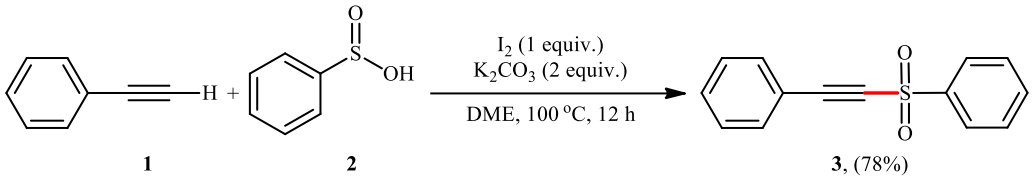
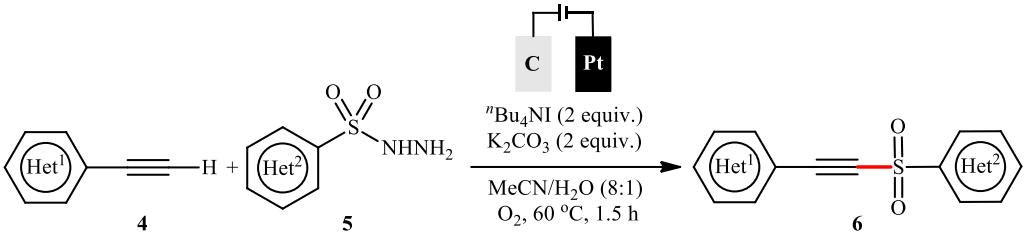


Fig. 1. Direct sulfonylation of terminal acetylenes and acetylenic acids.



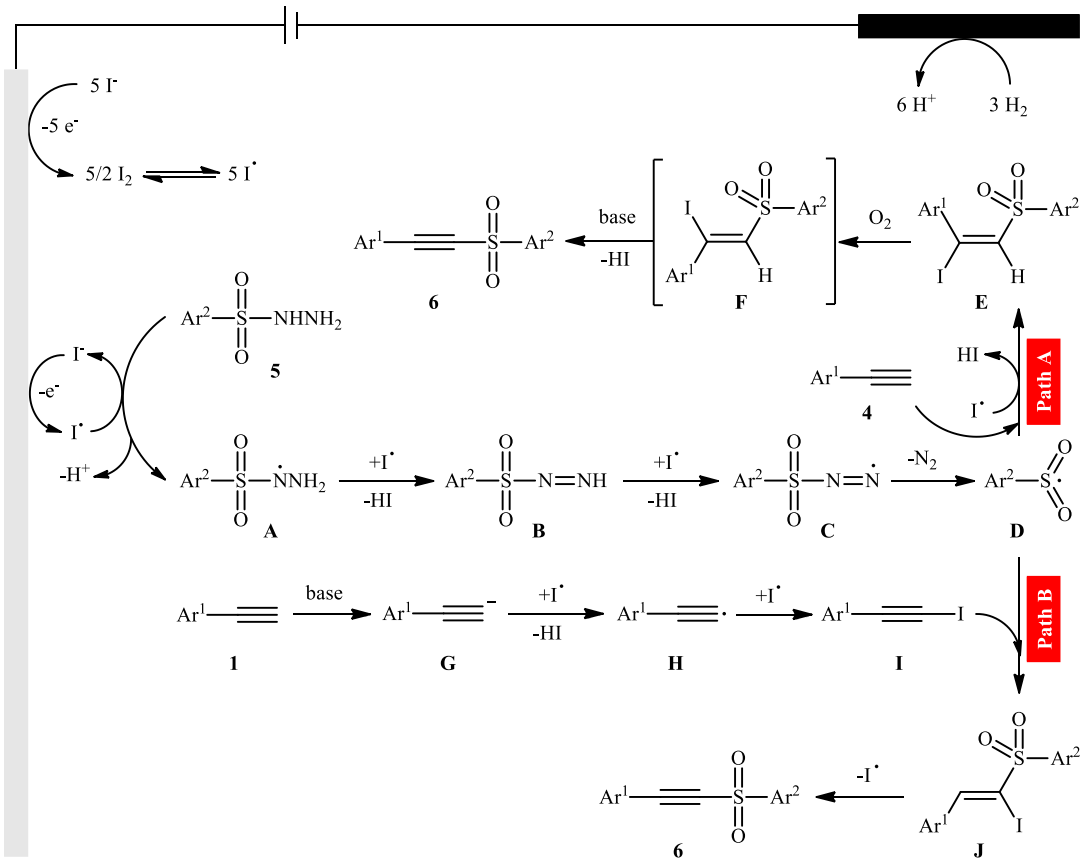
Scheme 1. Wang's synthesis of ((phenylethynyl)sulfonyl)benzene 3.



(Het)Ar^1= 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CO_2Me-C_6H_4, 4-CF_3-C_6H_4, 2-Me-C_6H_4, 2-naphthyl, 2-thienyl

(Het)Ar^2= Ph, 4-Me-C_6H_4, 4-Ph-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 2-Me-C_6H_4, 2-naphthyl, 2-thienyl

Scheme 2. Huang-Tang's synthesis of acetylenic sulfones **6**.



Scheme 3. Mechanistic proposal for the formation of acetylenic sulfones **6**.

Very recently, Cheng and colleagues developed an elegant visible light-mediated photoredox-catalyzed sulfonylation of terminal (hetero)aromatic alkynes **7** with (hetero)aryl sulfonylhydrazides **8** using molten-salt method derived carbon nitride (MCN) as a transition metal-free polymeric photocatalyst, KI as an additive, and K_2CO_3 as a base [23]. The reactions proceeded in acetone under 420 nm LED irradiation at room temperature in O_2 atmosphere, giving moderate to high yields of the desired acetylenic sulfones **9** within 2 h (Scheme 4). Notably, the success of this reaction was strongly depended on the presence of both the catalyst and light. No product was formed when either was absent. Furthermore, the reaction atmosphere played a crucial

role in the success of this transformation, as conducting the process under air or nitrogen atmosphere resulted in no product formation.

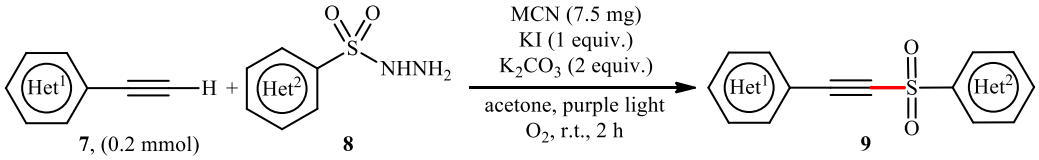
In this study, the authors showcased a broad scope for both (hetero)aromatic alkynes and (hetero)aryl sulfonylhydrazides. However, the applicability of aliphatic alkynes and alkyl sulfonylhydrazides as starting materials was not explored. Interestingly, guided by the same principle, a similar C-H sulfonylation strategy was successfully applied towards the synthesis of a library of vinyl sulfones from the respective terminal alkenes. After conducting a series of mechanistic investigations, the authors suggested that this C-S bond forming reaction most likely proceeds through a radical pathway, as depicted in Scheme 5.

2.3. Sodium sulfinates as sulfonylation agents

In 2016, Kuhakarn and co-workers disclosed the effectiveness of sodium sulfinates as sulfonylation agents in the direct C–H sulfonylation of terminal alkynes [24], when phenylacetylene derivatives 10 underwent selective sulfonylation with a series of sodium aryl sulfinates 11 in the presence of 1 equiv. of I_2 and 3 equiv. of TBHP in THF under ambient conditions to form corresponding acetylenic sulfones 12 with yields ranging from 17% to 68% (Scheme 6).

The results showed that the electronic effects of the substituents on both coupling partners had a significant influence on the reaction outcome.

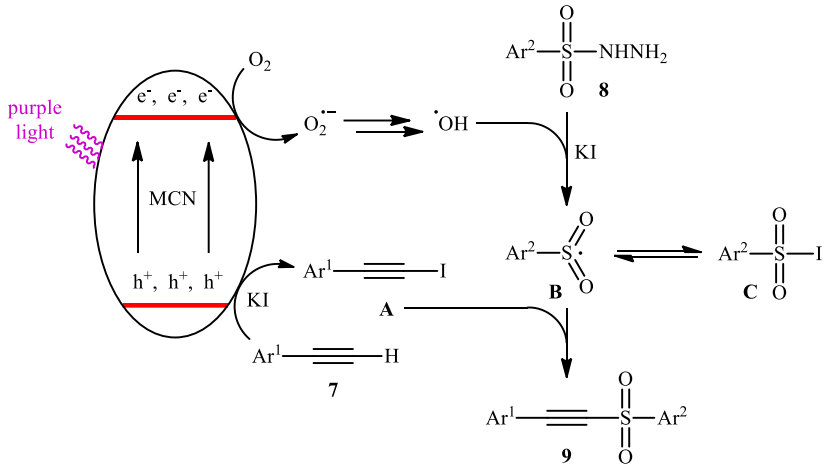
Generally, the best yields were obtained with electron-rich substrates. Notably, under the standard reaction conditions, terminal aliphatic alkynes did not yield alkylacetylenic sulfones but instead formed the corresponding (*E*)-β-iodovinyl sulfones in low yields. Likewise, internal alkynes also yielded the (*E*)-β-iodovinyl sulfones under the same conditions, though with similarly low efficiency.



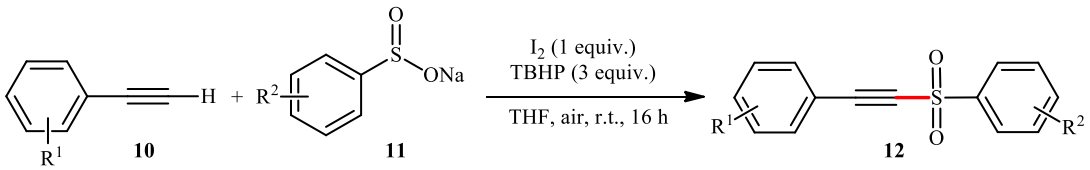
(Het)Ar^1= Ph, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-CN-C_6H_4, 4-CF_3-C_6H_4, 4-CO_2Me-C_6H_4, 3-Br-C_6H_4, 2-Me-C_6H_4, 2-OMe-C_6H_4, 2-naphthyl, 2-thienyl

(Het)Ar^2= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 2-naphthyl, 2-thienyl

Scheme 4. Cheng's synthesis of acetylenic sulfones **9.**



Scheme 5. Proposed mechanism for the formation of acetylenic sulfones 9.



R^1= H, 4-Me, 4-OMe, 4-F, 3-F, 2-Br

R^2= H, 4-Me, 4-OMe, 4-Cl, 4-Br

Scheme 6. Kuhakarn's synthesis of acetylenic sulfones 12.

Afterwards, Huang's group introduced an interesting strategy for the synthesis of acetylenic sulfones 15 through the electrochemical sulfonylation of aromatic alkynes 13 with sodium aryl sulfinates 14 [25].

The authors studied the effects of reaction variables such as electrolyte, electrode, current, and solvent and found that performing the reaction in an undivided cell under a constant current of 10 mA with platinum plates as electrodes employing KI as the electrolyte and aqueous acetonitrile as the solvent at room temperature was the optimum reaction condition. Under optimized conditions, the reaction tolerated various electron-donating and electron-withdrawing substituents at various substitution sites of both reaction components and gave corresponding acetylenic sulfones 15 in low-to-high yields (Scheme 7).

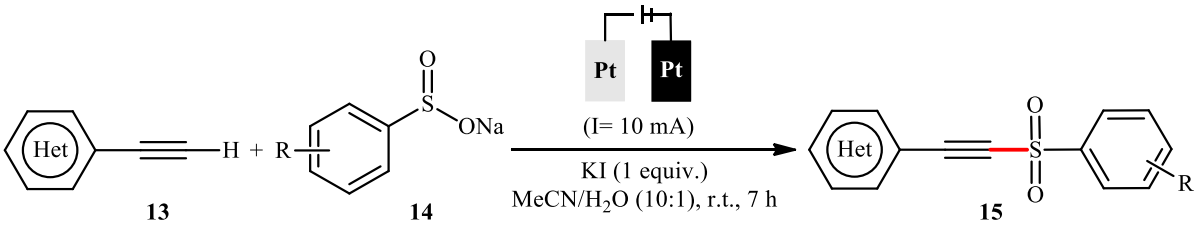
Notably, this methodology was also effectively applied to the late-stage sulfonylation of an estrone-derived alkyne. The results demonstrated that terminal phenylacetylenes with electron-donating groups were more efficient than those with electron-withdrawing groups, and the substitution patterns at the *ortho*-, *meta*-, and *para*-positions had little impact on the reaction performance. Similarly, sodium aryl sulfinates bearing electron-donating substituents afforded better yields compared to the electron-withdrawing group containing substrates. The coupling of sodium aryl sulfinates (*e.g.*, sodium ethanesulfinate) was feasible under the standard conditions, albeit in poor yields.

2.4. Thiosulfonates as sulfonylation agents

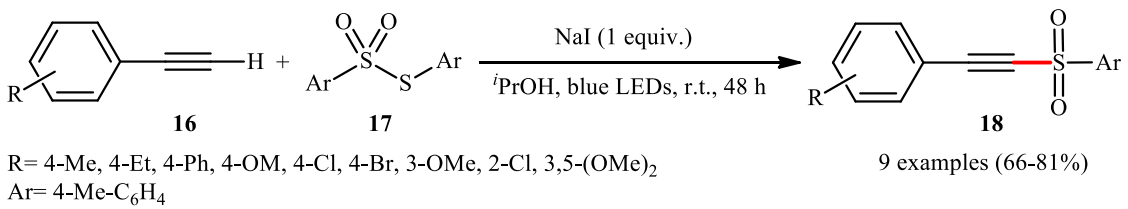
Recently, Jiang and Li along with their co-workers reported the first example of direct and selective $C_{(alkynyl)}$–H sulfonylation of terminal alkenes with symmetrical thiosulfonates as sulfonyl sources under visible light irradiation at room temperature, which allows for high yielding preparation of functionalized acetylenic sulfones [26]. The optimized reaction conditions were established using NaI as the iodine source, blue LEDs as the light source, and ^{i}PrOH as the reaction medium. Under the optimized conditions, a series of phenylacetylene derivatives 16 underwent successful C–S coupling with *S*-*p*-tolyl 4-methylbenzenesulfonothioate 17, affording good to high yields of the corresponding acetylenic sulfones 18 (Scheme 8).

These authors demonstrated a relatively broad scope for the alkenes, but the scope of the thiosulfonate substrate was very limited, with only one being tested. It is worth mentioning that under similar conditions, the sulfonylation of a diverse range of styrene derivatives with various symmetrical aryl thiosulfonates were also proceeded effectively to afford the corresponding vinyl sulfones in modest to excellent yields.

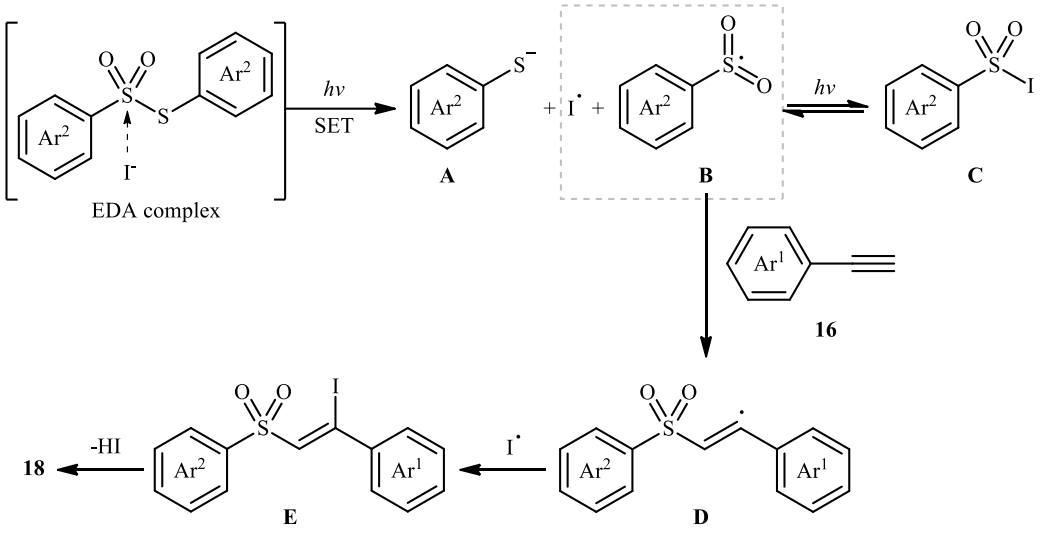
On the basis of a series of mechanism studies and previous works, it was suggested that this sulfonylation reaction starts with the generation of an electron-donor–acceptor (EDA) complex between the thiosulfonate 17 and NaI, which then undergoes single electron transfer to form the sulfur anion PhS^{-} A, the sulfonyl radical B, and the iodine radical under light irradiation. Subsequently, the sulfonyl radical B reacts with phenylacetylene 16 to produce the vinyl radical D, that after coupling with iodine radical affords species E. Finally, elimination of HI from E in the presence of base gives the observed product 18 (Scheme 9).



Scheme 7. Huang's synthesis of acetylenic sulfones 15.



Scheme 8. Jiang-Li's synthesis of acetylenic sulfones 18.



Scheme 9. Mechanistic proposal for the formation of acetylenic sulfones 18.

3. Decarboxylative sulfonylation of acetylenic acids

Decarboxylative cross-coupling reactions are one of the most attractive and powerful strategies for the construction of C–C/X bonds [27]. These reactions provide several advantages, such as mild conditions, broad substrate scope, and minimal waste, making them a highly efficient and environmentally friendly alternative to traditional cross-coupling methods. In 2019, Hosseinian and co-workers published an insightful review paper entitled "A walk around the decarboxylative C-S cross-coupling reactions" which highlights some of key investigations into the construction of carbon-sulfur bonds *via* decarboxylative cross-coupling reactions between carboxylic acids and sulfur-containing coupling partners [28].

However, at that time, only a single example had been reported on the synthesis of acetylenic sulfones through the decarboxylative sulfonylation of the corresponding acetylenic acids. Given the significant progress and advancements in this research area over the past few years, it is an appropriate time to compile these developments into an updated and comprehensive review. In the current section, we summarize the available literature on the titled reactions, classifying it based on the type of sulfonylating agents used.

3.1. Sulfonyl hydrazides as sulfonylation agents

The first and only report on the decarboxylative sulfonylation of acetylenic acids using sulfonyl hydrazides was published by Singh *et al*. in 2015 [29], who demonstrated that the treatment of phenylpropiolic acid 19 with arylsulfonyl hydrazides 20 in the presence of a combination of I_2, DBU, and TBHP in aqueous acetonitrile under an air atmosphere let to the formation of acetylenic sulfones 21 in good yields (Scheme 10). Although only two examples were disclosed, this paper represents the first-ever example of decarboxylative sulfonylation of alkynyl C-CO_2H bonds. Notably, besides propiolic acids, cinnamic acids also could be applied as suitable substrates under the identical conditions. Mechanistically, the arylsulfonyl radical was initially generated in situ from sulfonyl hydrazides with the release of N_2 under oxidative conditions. The resulting sulfonyl radical then selectively added to the carbon atom adjacent to the carboxyl group in propiolic acid, forming a vinyl radical intermediate. Subsequently, an iodine-catalyzed decarboxylation process led to the formation of the observed acetylenic sulfone products.

3.2. Sodium sulfinates as sulfonylation agents

The first example of the decarboxylative sulfonylation of acetylenic acids using sodium sulfinates was reported by Kuhakarn and co-workers in 2016 [30]. By using molecular iodine as a catalyst and TBHP as an oxidant in THF, various (hetero)aryl propiolic acids 22 smoothly underwent decarboxylative sulfonylation with sodium sulfinates 23 to afford the corresponding acetylenic sulfones 24 in poor to excellent yields (Scheme 11).

Some important information of this synthetic procedure is listed below: (i) aryl propiolic acids bearing electron-releasing substituents gave higher yields in comparison to those bearing electron-withdrawing substituents; (ii) β-alkyl- and β-silyl-substituted propiolic acids failed to participate in this transformation; (iii) sodium aryl sulfinates with electron-donating substituents gave higher yield of products than sodium aryl sulfinates with electron-withdrawing substituents; (iv) sterically hindered sodium aryl sulfinates (e.g., sodium mesitylenesulfinate) and strongly electron deficient sulfinates (e.g., sodium 2,4-dinitrobenzenesulfinate and sodium trifluoromethanesulfinate) failed to produce any product under the optimized conditions; and (v) sodium alkyl sulfinates were also amenable substrates in this reaction, albeit diverting to the corresponding acetylenic sulfone in

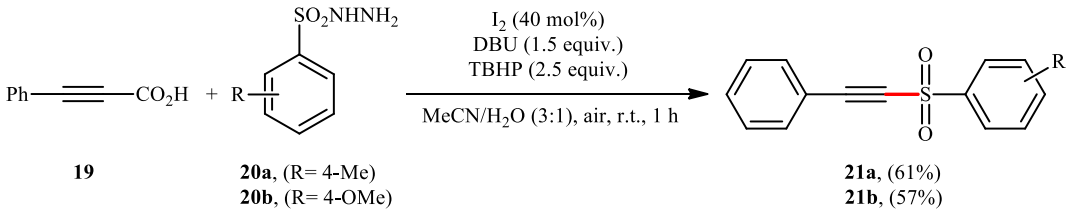
low yields. Based on a series of control experiments and the literature, the authors proposed two possible mechanisms for the formation of acetylenic sulfones 24, as illustrated in Scheme 12. In pathway A, the oxidation of sodium sulfinate 23 in the presence of iodine and TBHP results in the formation of the oxygen-centered sulfonyl radical A, which is in equilibrium with the sulfur-centered sulfonyl radical B. Subsequently, sulfonyl radical B directly adds to propiolic acid 22, generating the vinyl radical intermediate E. Finally, the decarboxylation of intermediate E leads to the final product 24. On the other hand, in pathway B, the reaction of iodine with TBHP generates a more reactive electrophilic iodine species, which subsequently reacts with sodium sulfinate 23 to form sulfinylhypoiodite C. This intermediate exists in equilibrium with its corresponding sulfonyl iodide D, which, upon homolytic cleavage, first generates the oxygen-centered sulfonyl radical A and eventually converts into the sulfur-centered sulfonyl radical B. Four years later, an electrochemical version of this sulfonylation reaction was developed by Zhong *et al*. [31].

They disclosed that the treatment of various aryl propiolic acids 25 with sodium aryl sulfinates 26 in an undivided cell, equipped with a graphite rod anode and a platinum plate cathode, under a constant current of 20 mA at room temperature, provided the corresponding acetylenic sulfones 27 in moderate yields, ranging from 32% to 62%. As shown in Scheme 13, the reaction exhibited relatively good tolerance to a range of electron-donating and electron-withdrawing functional groups on both coupling partners. However, the applicability of alkyl propiolic acids and sodium alkyl sulfinates as starting materials was not explored in this study. In Scheme 14, a plausible mechanistic pathway for this decarboxylative sulfonylation is proposed. Initially, sodium sulfinate 26 undergoes single-electron transfer (SET) oxidation at the anode to generate the sulfonyl radical intermediate A. This intermediate A then attacks the arylacetylenic acid anion 25 to form radical intermediate B. Finally, decarboxylation of intermediate B affords the observed acetylenic sulfones 27.

Subsequently, Jia and co-workers developed this chemistry using a novel nano-photocatalyst BiOCl/cellulose nanocrystal (CNC) [32]. Thus, with the assistance of a catalytic amount of BiOCl/CNC and one equivalent I_2, a range of (hetero)aryl propiolic acids 28 reacted with sodium aryl sulfinates 29 under an oxygen atmosphere and visible light irradiation to afford the target acetylenic sulfones 30 in poor to almost quantitative yields (Scheme 15). Although the reaction exhibited good tolerance toward a series of electron-donating functional groups on aryl propiolic acids, its efficiency was markedly reduced when applied to electron-deficient aryl propiolic acids. Moreover, highly sterically hindered sodium aryl sulfinates such as sodium mesitylenesulfinate failed to participate in this reaction.

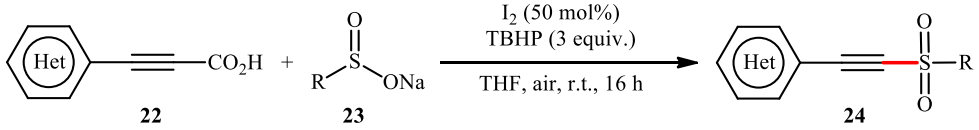
3.3. *N*-Hydroxy sulfonamides as sulfonylation agents

In 2021, Raghuvanshi and Verma demonstrated the coupling of phenylpropiolic acid 19 with *N*-hydroxy aryl sulfonamides 31 to yield the corresponding acetylenic sulfones 32 through I_2-mediated decarboxylative sulfonylation [33]. The optimized conditions employed 1 equiv. I_2 as a mediator together with 1 equiv. of K_2CO_3 as a base. The reactions were carried out in EtOH under an air atmosphere and provided the expected sulfones in good yields within 6 h (Scheme 16). Regrettably, this preliminary study included only four reported examples, and the substrate scope of the reaction remained largely unexplored.



19 **20a**, (R= 4-Me) **20b**, (R= 4-OMe) **21a**, (61%) **21b**, (57%)

Scheme 10. Singh's synthesis of acetylenic sulfones 21.

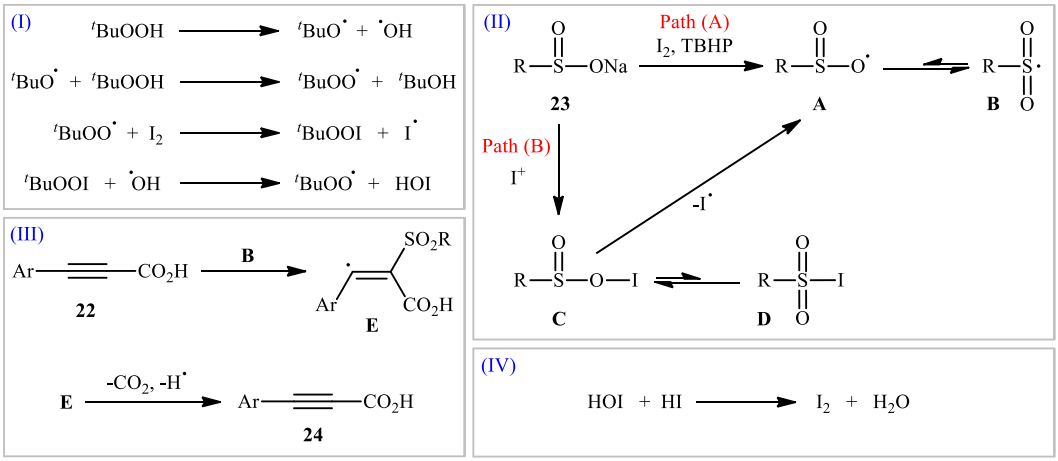


22 **23** **24**

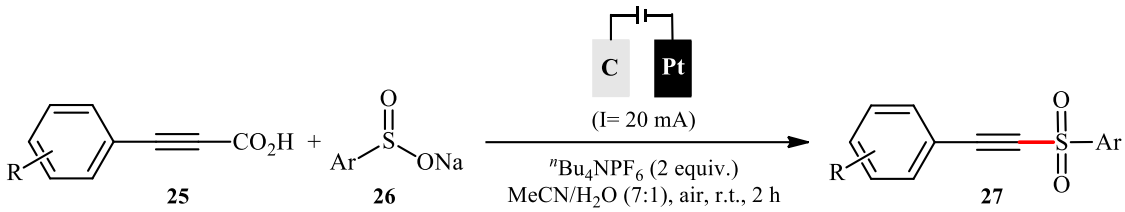
19 examples (20-90%)

(Het)Ar= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4, 2-Br-C_6H_4, 2,4-$(OMe)_2$-C_6H_3, 2-Me-4-OMe-C_6H_3, 2-naphthyl, 2-thienyl
R= Me, Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

Scheme 11. Kuhakarn's synthesis of acetylenic sulfones 24.

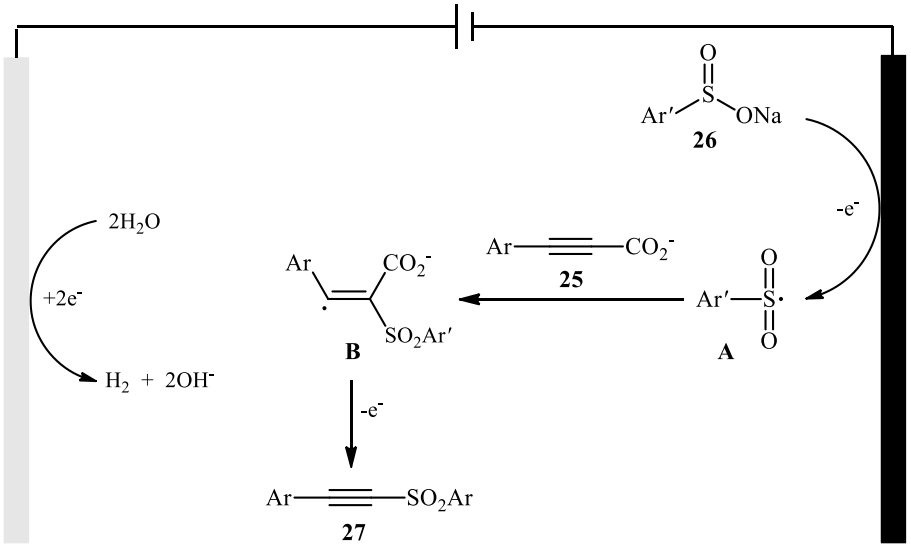


Scheme 12. Plausible mechanism for the reaction in Scheme 11.

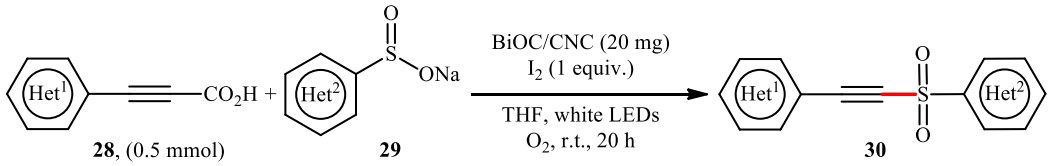


R= H, 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 3-Me, 3-OMe, 2-Me, 2-OMe, 2-Cl, 3,5-$(Me)_2$, 2,3-$(CH{=}CH)_2$-
Ar= Ph, 4-Me-C_6H_4, 4-CF_3-C_6H_4, 2-Cl-C_6H_4

Scheme 13. Zhong's synthesis of acetylenic sulfones 27.



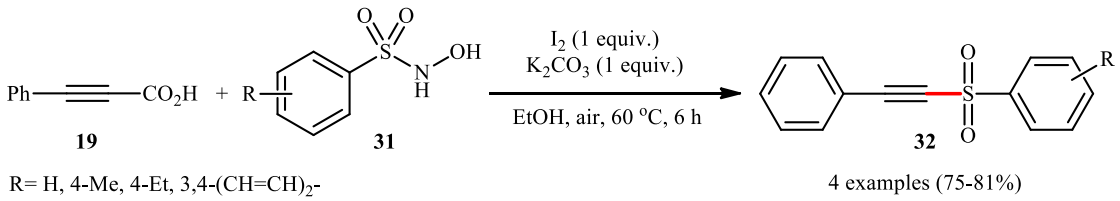
Scheme 14. Proposed mechanism for the formation of acetylenic sulfones 27.



(Het)Ar^1= Ph, 4-Me-C_6H_4, 4-Ph-C_6H_4, 4-OMe-C_6H_4, 4-CF_3-C_6H_4, 3-OMe-C_6H_4, 2-Me-C_6H_4, 2-naphthyl, 2-thienyl
(Het)Ar^2= Ph, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Br-C_6H_4, 2-Br-C_6H_4, 2-naphthyl, 2-thienyl

19 examples (26-96%)

Scheme 15. Jia's synthesis of acetylenic sulfones 30.



Scheme 16. Raghuvanshi-Verma's synthesis of acetylenic sulfones 32.

4. Conclusion

The direct sulfonylation of terminal acetylenes and the decarboxylative sulfonylation of acetylenic acids offer novel and efficient methods for synthesizing biologically and synthetically important acetylenic sulfone derivatives. By bypassing the need for pre-functionalization of the substrates, these reactions are cleaner, safer, and faster compared to conventional methods for the synthesis of the titled compounds. However, these areas still require further investigation due to several challenges and limitations in the existing reports. For example: (i) most reported examples are focused on aromatic substrates, so expanding the scope of these protocols to include aliphatic substrates is essential; (ii) the scope of sulfonylation agents is narrow and primarily limited to sulfinate salts and sulfonylhydrazides. Therefore, exploring the use of other sulfonylating reagents (such as sulfonyl chlorides) in these transformations is necessary; and (iii) many of the reactions covered in this review have been conducted in the presence of an iodinating agent. Hence, there is a continued need to investigate and discover novel catalytic systems that can enable these reactions under halogen-free conditions.

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