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Recent advances in sulfonylation reactions using potassium/sodium metabisulfite

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Recently, sulfonylation reactions using potassium/sodium metabisulfite as the sulfur dioxide surrogate have been developed rapidly. In most cases, the transformations go through radical processes with the insertion of sulfur dioxide under mild conditions. Additionally, transition metal catalysis is applied in the reactions for the synthesis of sulfonyl-containing compounds. Among the approaches, photoinduced conversions under visible light or ultraviolet irradiation are also involved. In this updated report, the insertion of sulfur dioxide from potassium metabisulfite or sodium metabisulfite is summarized.

1. Introduction

It is known that sulfonyl-containing compounds are important in the field of pharmaceuticals and materials science.¹ Fig. 1 presents some examples of sulfonyl-containing drug molecules

on the market.² Thus, continuous efforts have been made in the synthesis of sulfonyl compounds including sulfones and sulfonamides. So far, there are many conventional methods for the generation of sulfonyl compounds.³ For example, sulfonated indolo[1,2-*a*]quinolines with excellent fluorescence properties could be synthesized from arylsulfonyl hydrazides and 1-(2-(arylethynyl)phenyl)indoles in the presence of TBAI/TBHP.^{3f} Recently, the focus has been centered on the insertion of sulfur dioxide.⁴ In the past decade, several sulfur dioxide surrogates have been used as the source of sulfur dioxide in organic transformations. For instance, the bench-stable reagent of 1,4-diazabicyclo[2.2.2]octane-sulfur dioxide (DABCO-(SO₂)₂), as initially disclosed by Santos and Mello in 1988,⁵ has been used

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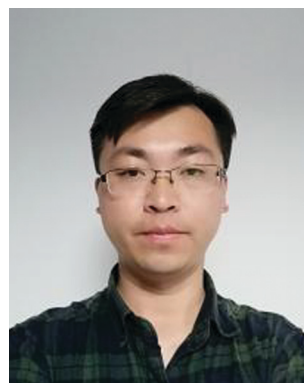
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the School of Pharmaceutical and Materials Engineering at Taizhou University as an associate professor. He got the Thieme Chemistry Journals Award in 2020. Currently, his research interests mainly focus on the development of new methods for the synthesis of bioactive compounds.



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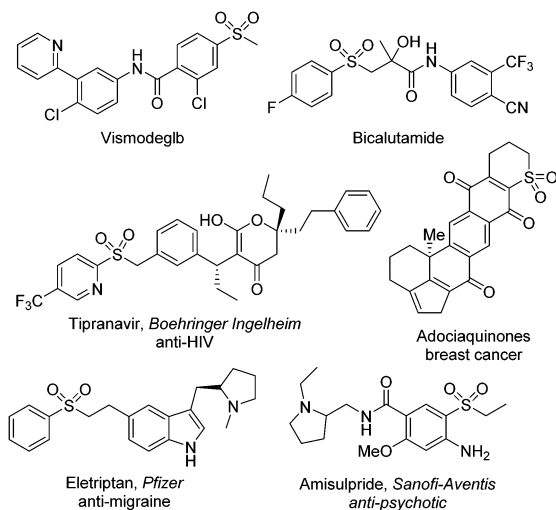
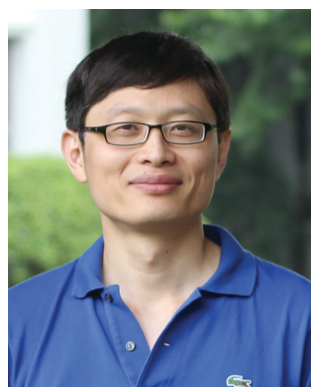


Fig. 1 Marketed sulfonyl-containing drugs.

broadly as the source of sulfur dioxide⁶ although the preparation of DABCO·(SO₂)₂ suffers from harsh reaction conditions from gaseous sulfur dioxide at -78 °C.

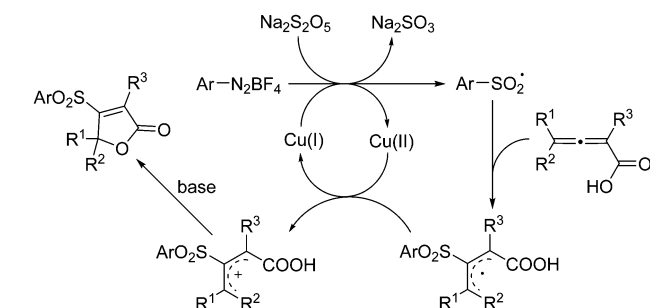
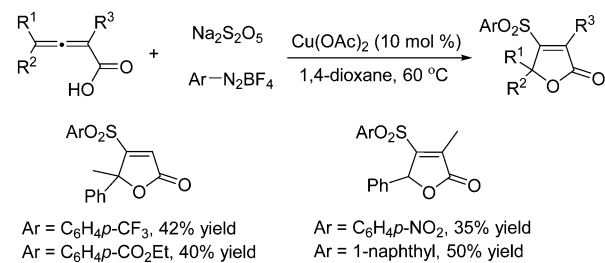
Inorganic sulfites as another sulfur dioxide surrogate have attracted continuous interest, because inorganic sulfites are easily available, cheap and abundant in nature. Since the first example of using potassium metabisulfite as the source of sulfur dioxide in the palladium-catalyzed sulfonylation of aryl halides with hydrazines as described by Wu and co-workers in 2012,⁷ significant progress for the synthesis of sulfonyl-containing compounds by using potassium/sodium metabisulfite has been witnessed. Among the inorganic sulfites screened, potassium/sodium metabisulfite was demonstrated as the most efficient one. At the end of 2018, the insertion of sulfur dioxide from potassium metabisulfite or sodium metabisulfite was summarized,^{4j} since inorganic sulfites



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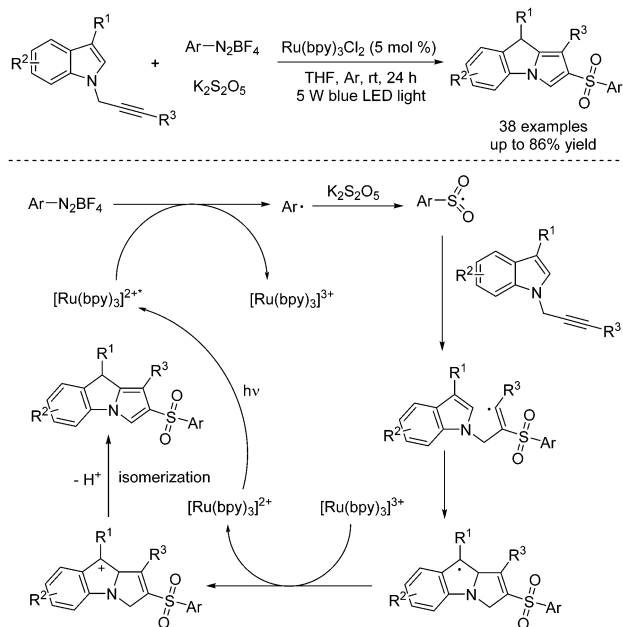


Scheme 1 A copper(II)-catalyzed multicomponent reaction of 2,3-allenoic acids, sodium metabisulfite and aryl diazonium tetrafluoroborates.

would be ideal as the source of sulfur dioxide in organic transformations. From 2019, methods developed using potassium/sodium metabisulfite in sulfonylation reactions boomed. In most cases, the transformations went through radical processes with the insertion of sulfur dioxide under mild conditions. Additionally, transition metal catalysis was applied in the reactions for the synthesis of sulfonyl-containing compounds. Among the approaches, photoinduced conversions under visible light or ultraviolet irradiation were also involved. In this updated report, we herein report the recent advances in sulfonylation reactions using potassium/sodium metabisulfite as the source of sulfur dioxide from Dec. 2018.

2. Sulfonylation from aryl diazonium tetrafluoroborates and potassium/sodium metabisulfite

The combination of DABCO·(SO₂)₂ with aryl diazonium tetrafluoroborates was demonstrated efficiently for the generation of the arylsulfonyl radical and tertiary amine (DABCO) radical cation under mild conditions *via* single electron transfer.⁸ Potassium/sodium metabisulfite was applied as well in the reaction of aryl diazonium tetrafluoroborates as a replacement for DABCO·(SO₂)₂. It is known that the scaffold of the furan-2(5*H*)-one core broadly exists in biologically active natural products, pharmaceuticals, and pesticides.⁹ Additionally, furan-2(5*H*)-ones are useful building blocks in organic synthesis for the construction of complex molecules.¹⁰ Starting from sodium metabisulfite, 4-sulfonylated furan-2(5*H*)-ones could be easily prepared from a copper(II)-catalyzed multicomponent reaction of 2,3-allenoic acids and aryl diazonium tetrafluoroborates under mild conditions (Scheme 1).¹¹ This method is quite effective under mild conditions, giving rise to

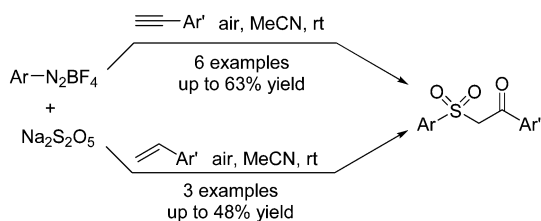


Scheme 4 Photoinduced reaction of aryldiazonium tetrafluoroborates, potassium metabisulfite and *N*-propargylindoles.

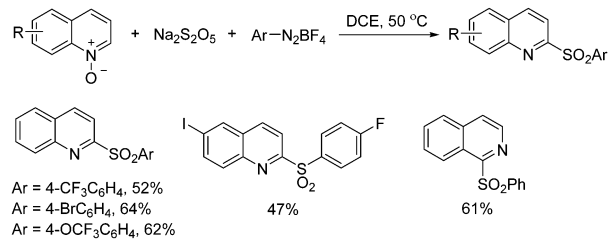
via single electron transfer. Then aryl radical would react with potassium metabisulfite, leading to the arylsulfonyl radical, which would attack the triple bond of *N*-propargylindole, giving rise to a vinyl radical intermediate. Intramolecular cyclization would subsequently occur. Following oxidative single electron transfer, the cation intermediate would be formed, which would undergo deprotonation and isomerization to produce the cyclic product.

Singh and co-workers described a multicomponent reaction for the synthesis of β -keto sulfones through a reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, and styrenes or alkynes (Scheme 5).¹⁷ Potassium metabisulfite or DABCO-(SO₂)₂ was used as the source of sulfone. Mechanistic studies from controlled liquid chromatography-mass spectrometry and ¹⁸O-labelling experiments revealed that the source of the incoming oxygen atom of the keto group in β -keto sulfones was from the air.

Xia and co-workers developed a metal-free three-component reaction of quinoline *N*-oxides, sodium metabisulfite and aryldiazonium tetrafluoroborates via a radical process (Scheme 6).¹⁸ 2-Sulfonyl quinolines or isoquinolines were obtained in moderate to good yields under mild conditions. On the basis of control experiments and literature reports, it was reasoned that aryldiazonium tetrafluoroborate would go through a decomposition



Scheme 5 Synthesis of β -keto sulfones through a reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, and styrenes or alkynes.



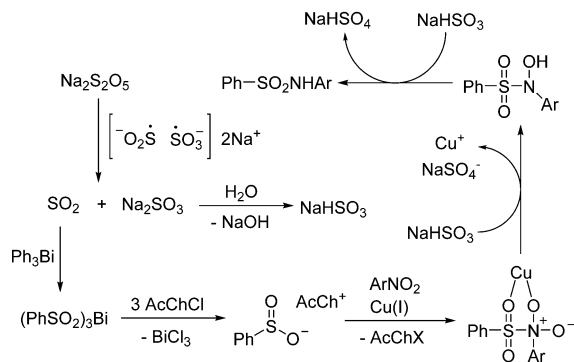
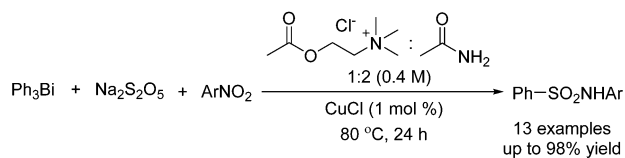
Scheme 6 Metal-free three-component reaction of quinoline *N*-oxides, sodium metabisulfite and aryldiazonium tetrafluoroborates.

process leading to the aryl radical, which would subsequently react with sodium metabisulfite to provide the arylsulfonyl radical. This arylsulfonyl radical would attack the quinoline *N*-oxide via a Minisci-like radical transformation. The resulting *O*-radical would capture another arylsulfonyl radical, with the following release of arylsulfonic acid to furnish the corresponding 2-sulfonylquinolines.

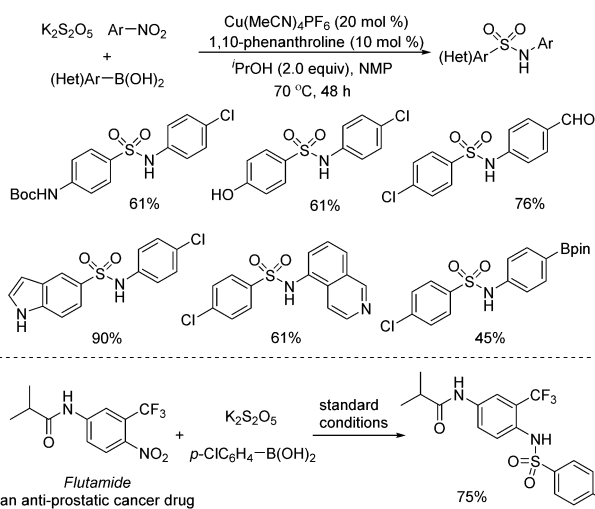
3. Sulfonylation from organometallic reagents and potassium/sodium metabisulfite

As basic raw chemical materials, nitroarenes are widely applied in the pharmaceutical, pesticide, and dye industries.¹⁹ So far, applications of nitroarenes have been extensively explored in synthetic chemistry. It was found that nitroarenes could be used as the coupling partner with sulfur dioxide for the preparation of sulfonamides. Synthesis of sulfonamides through a copper-catalyzed reaction of triarylboranes, sodium metabisulfite, and nitro compounds was developed by using a deep eutectic solvent as a reaction medium, as reported by Guillena and J. Ramón (Scheme 7).²⁰ In this transformation, triarylboranes were used as the substrates for the incorporation of sulfur dioxide into organic motifs, and the utilization of a deep eutectic solvent as a reaction medium was crucial for the conversion. A plausible mechanism was proposed, indicating that the insertion of sulfur dioxide from sodium metabisulfite into triarylborane would be the first step. Subsequently, arylsulfinate would be formed with the release of BiCl₃. In the presence of a copper catalyst, arylsulfinate would react with nitroarene. Following double reduction with NaHSO₃, the corresponding sulfonamide would be furnished (Scheme 3).

Later, Wu and co-workers described a copper-catalyzed reaction of arylboronic acids, nitroarenes, and potassium metabisulfite (Scheme 8).²¹ A range of sulfonamides was afforded in good to excellent yields. Broad substrate scope was demonstrated, and various functional groups including hydroxyl, cyano,



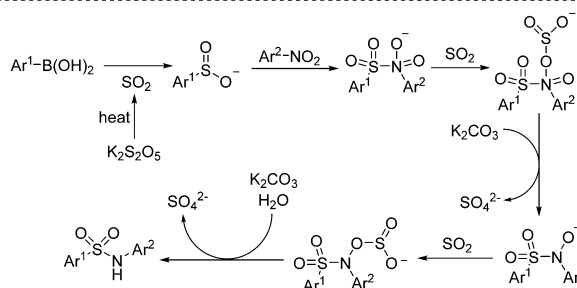
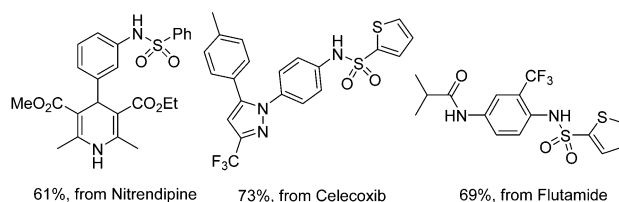
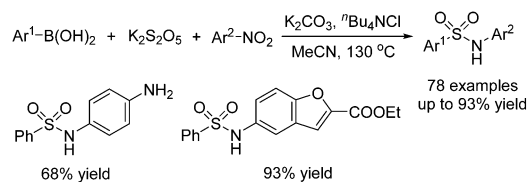
Scheme 7 Copper-catalyzed reaction of triarylbismuthines, sodium metabisulfite, and nitroarenes in a deep eutectic solvent.



Scheme 8 Copper-catalyzed reaction of arylboronic acids, nitroarenes, and potassium metabisulfite.

amino, and carbonyl were all compatible. Mechanistic studies showed that arylsulfonate was the intermediate, which was generated from the copper-catalyzed transmetalation of arylboronic acid and subsequent insertion of sulfur dioxide. The copper-assisted interaction of nitroarene and arylsulfonate was also the key for success. In this transformation, better results were obtained when isopropanol was used as the reductant. The late-stage modification of a currently marketed drug (Flutamide) was performed as well.

In the meantime, Chen, Wu, and co-workers described a one-pot three-component reaction of nitroarenes, (hetero)arylboronic acids, and potassium metabisulfite for the synthesis of sulfonamides (Scheme 9).²² Interestingly, this transformation went through sequential C–S and S–N coupling under metal catalyst-free conditions, although a high temperature was required. A broad reaction scope was present, and a range of substrates was

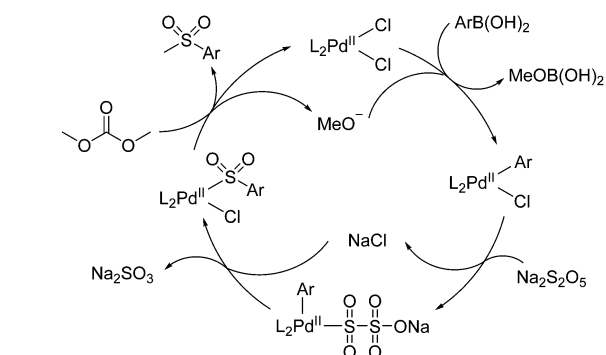
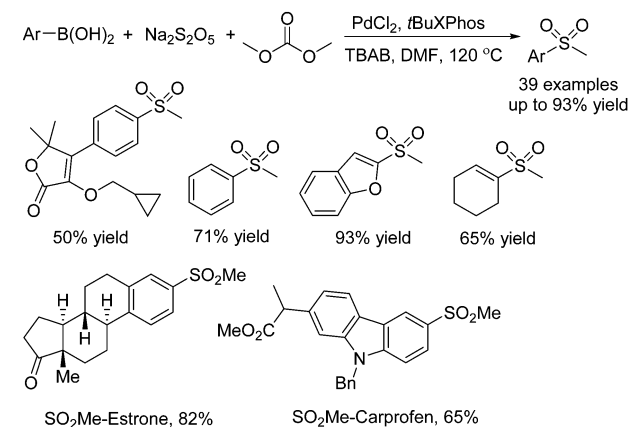


Scheme 9 One-pot reaction of nitroarenes, (hetero)arylboronic acids, and potassium metabisulfite.

examined under the conditions. It was proposed that at the outset, this reaction proceeded through nucleophilic addition of arylboronic acid to sulfur dioxide from potassium metabisulfite in the presence of a base, leading to arylsulfonate. Then arylsulfonate would react with nitroarene, followed by reduction of sulfur dioxide and double deoxygenation to produce the corresponding sulfonamide. This method was also successfully applied in the late-stage modification of currently marketed drugs (Scheme 9).

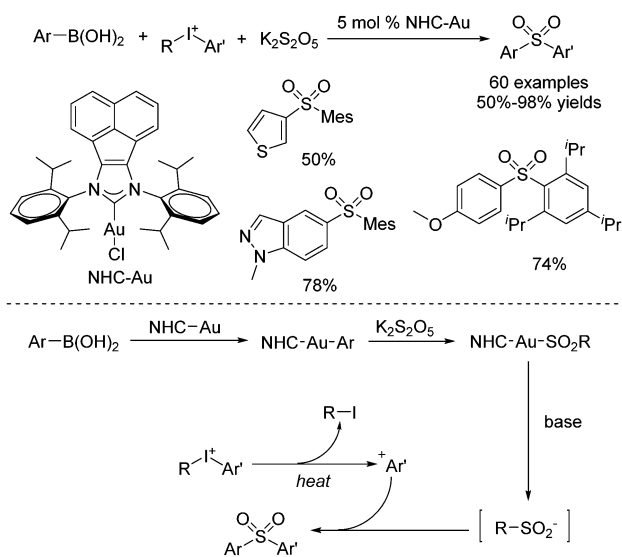
Due to the broad applications of methylsulfonyl-containing compounds in pharmaceuticals and bioactive molecules, methylsulfonylation for the generation of methylsulfonyl-containing compounds is one of the important transformations in organic synthesis. Jiang and co-workers reported another approach for the generation of methylsulfonyl-containing compounds. Diverse methyl sulfones could be prepared through a palladium-catalyzed three-component reaction of arylboronic acids, sodium metabisulfite, and dimethyl carbonate (Scheme 10).²³ Interestingly, dimethyl carbonate was used as the methyl reagent in this transformation. Additionally, the late-stage modification of pharmaceuticals and the synthesis of Firocoxib were efficiently established by using this strategy. Experimental evidence revealed that the radical pathway was excluded. It was postulated that the transmetalation of arylboronic acid with the palladium catalyst would occur firstly. Subsequently, sulfur dioxide insertion into the palladium complex would take place with the assistance of the electron-rich ligand. Finally, alkylation with dimethyl carbonate would produce the corresponding methyl sulfone product with the regeneration of the palladium catalyst.

Synthesis of *ortho*-substituted diarylsulfones through a reaction of arylboronic acids, potassium metabisulfite, and diaryliodonium

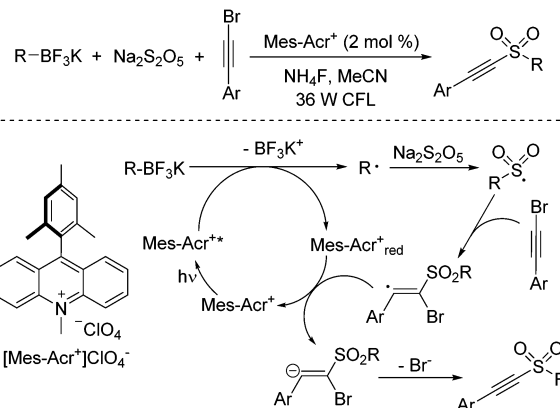


Scheme 10 Palladium-catalyzed three-component reaction of arylboronic acids, sodium metabisulfite, and dimethyl carbonate.

salts was established by using an acenaphthoimidazolydene gold complex as the catalyst (Scheme 11).²⁴ This sulfonylation process allowed the sterically hindered aryl groups in diaryliodonium salts to be preferentially transferred over less bulky ones. The chemoselectivity might be attributed to the more stable bulky Ar⁺ formed



Scheme 11 Synthesis of *ortho*-substituted diarylsulfones through a gold-catalyzed reaction of arylboronic acids, potassium metabisulfite, and diaryliodonium salts.



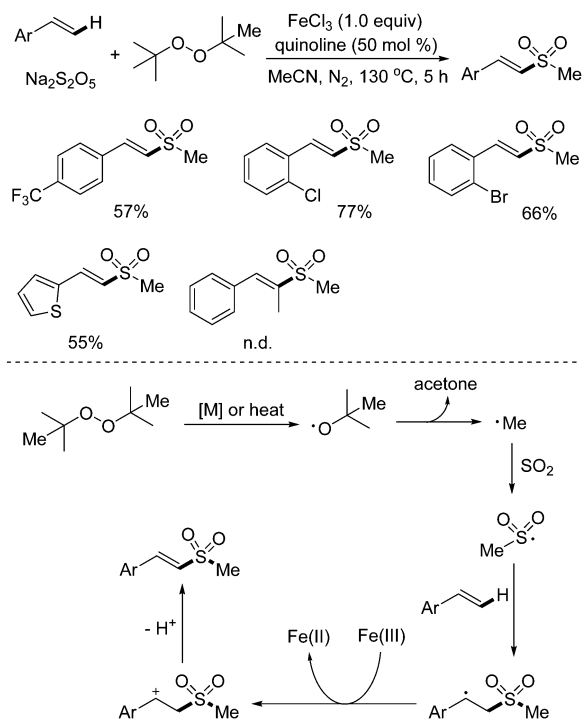
Scheme 12 Photoinduced reaction of potassium alkyltrifluoroborates, sodium metabisulfite, and alkynyl bromides.

by the diaryliodonium salt. Diverse (poly)-*ortho*-substituted diarylsulfones could be generated. The proposed mechanism showed that transmetalation of NHC-Au(I) species with arylboronic acid would occur to provide NHC-Au-Ar species, as reported by Toste.²⁵ Then sulfur dioxide insertion would take place to afford sulfonyl Au(I) complex NHC-Au-SO₂-Ar, which would further furnish an arylsulfonate intermediate.²⁵ Meanwhile, the more stable bulky Ar⁺ from the diaryliodonium salt would be captured by arylsulfonate, giving rise to a sterically hindered diarylsulfone.

Recently, radical processes initiated by the treatment of organotrifluoroborates under photoredox catalysis have developed rapidly.²⁶ In general, carbon radical species would be formed from organotrifluoroborates in the presence of a photocatalyst under visible light irradiation. Compared with aryldiazonium tetrafluoroborates, alkyl radicals would be produced from potassium alkyltrifluoroborates. Thus, a photoinduced reaction of potassium alkyltrifluoroborates, sodium metabisulfite, and alkynyl bromides under visible light irradiation at room temperature under photocatalysis was designed and developed (Scheme 12).²⁷ A broad substrate scope was presented, and diverse alkylalkynyl sulfones were generated in moderate to good yields. A similar mechanism was proposed, which showed that the alkyl radical was formed initially from potassium alkyltrifluoroborate in the presence of the photocatalyst under visible light irradiation. Subsequent sulfonylation and addition to alkynyl bromide would provide the final outcome. During the reaction, the presence of ammonium fluoride would enhance the reaction efficiency.

4. Others

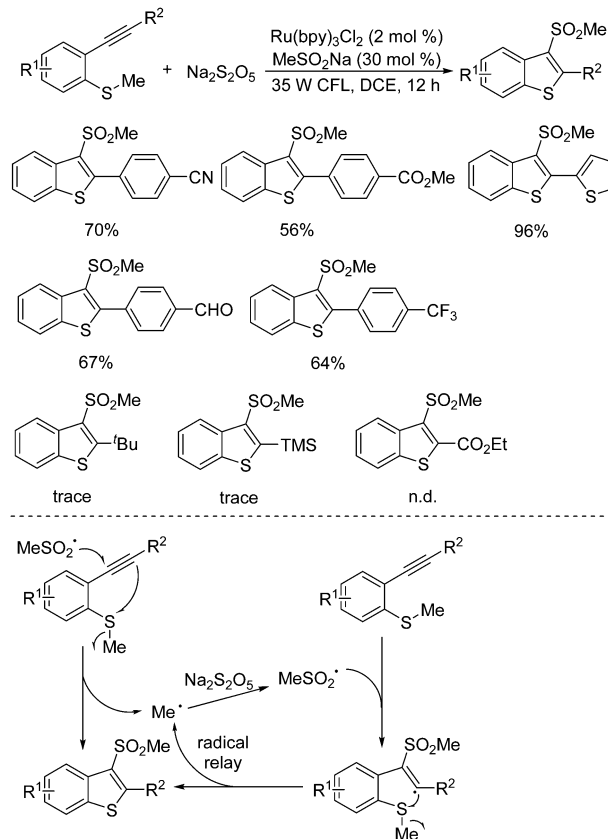
As mentioned above, methylsulfonylation for the generation of methylsulfonyl-containing compounds is one of important transformations in organic synthesis, especially for C-H bond methylsulfonylation. Recently, the synthesis of (*E*)-2-methyl styrenyl sulfones *via* direct C-H methyl sulfonylation of alkenes with sodium metabisulfite was developed (Scheme 13).²⁸ During the reaction process, di-*tert*-butyl peroxide (DTBP) was employed as the methyl source, and a range of (*E*)-2-methyl styrenyl sulfones were produced in good yields. In this transformation,



Scheme 13 Synthesis of (*E*)-2-methyl styrenyl sulfones via direct C–H methyl sulfonylation of alkenes with sodium metabisulfite.

1.0 equiv. of iron(III) chloride and a high temperature had to be used for successful conversion. It was postulated that the homolytic cleavage of DTBP would afford a *tert*-butyl radical, which would be further converted to a methyl radical and acetone. Then, the methyl radical would react with sodium metabisulfite, leading to a methylsulfonyl radical intermediate, which would attack the double bond of the alkene to produce a carbon radical species. With the assistance of iron(III), this carbon radical would be oxidized to a cation intermediate via single electron transfer (SET), which would subsequently undergo deprotonation to provide the desired (*E*)-2-methyl styrenyl sulfone.

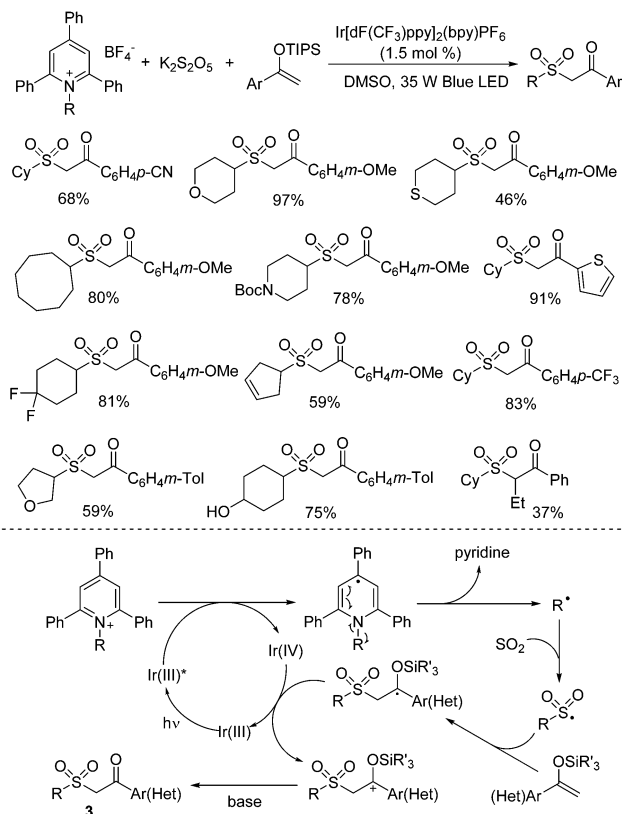
A radical relay strategy for the generation of 3-(methylsulfonyl)benzo[*b*]thiophenes was developed. This transformation starting from methyl(2-alkynylphenyl)sulfanes and sodium metabisulfite proceeded smoothly in the presence of a photocatalyst under visible light irradiation (Scheme 14).²⁹ Interestingly, a catalytic amount of sodium methylsulfinate was used as an initiator in this photoinduced sulfonylation process under mild conditions. The generality of this radical relay reaction was examined, and the corresponding 3-(methylsulfonyl)benzo[*b*]thiophenes were obtained in moderate to good yields. Several sensitive functional groups including chloro, bromo, fluoro, cyano, ester, and aldehyde were all compatible under the conditions. The R² group attached on the triple bond of the substrate was crucial for the successful transformation. It was found that only an aryl group was effective, and no desired product was obtained when the group at the R² position of the substrate was changed to 2-pyridinyl, *tert*-butyl, trimethylsilyl, or ester. On the basis of experimental evidence, the proposed mechanism showed that the methylsulfonyl radical generated *in situ* from methylsulfinate via single electron



Scheme 14 Generation of 3-(methylsulfonyl)benzo[*b*]thiophenes from methyl(2-alkynylphenyl)sulfanes and sodium metabisulfite.

transfer in the presence of the excited state of the photocatalyst would initiate the reaction, which would subsequently attack the triple bond of methyl(2-alkynylphenyl)sulfane to produce a methyl radical. This released methyl radical went through a radical relay with sulfur dioxide from sodium metabisulfite, giving rise to the corresponding 3-(methylsulfonyl)benzo[*b*]thiophene through a vinyl radical intermediate. During the reaction process, it was assumed that the aryl group at the R² position would stabilize the vinyl radical intermediate. The reaction of sodium metabisulfite under the standard conditions was further extended to the substrates of 1-methoxy-2-(phenylethynyl)benzene and *N,N*-dimethyl-2-alkynylaniline as a replacement for methyl(2-alkynylphenyl)sulfanes. However, the desired 3-(methylsulfonyl)benzo[*b*]furans and 3-(methylsulfonyl)indoles could not be formed.

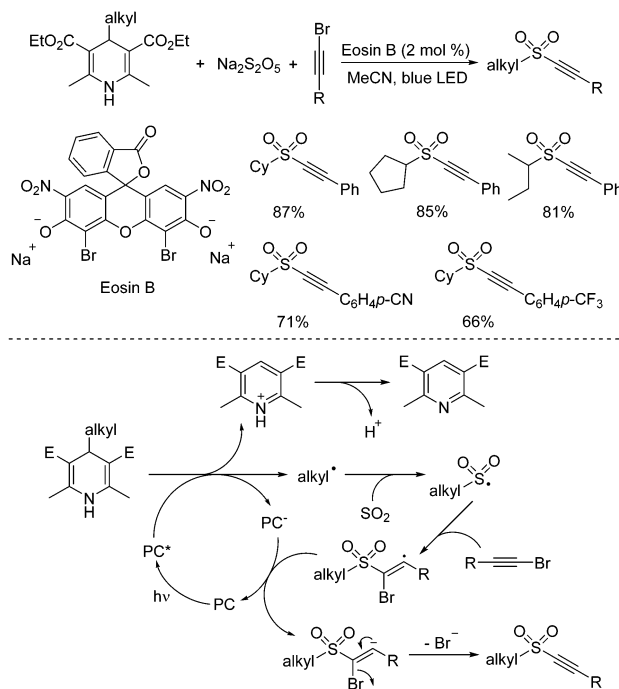
Recently, *N*-functionalized pyridinium salts such as Katritzky salts have been used as effective alkyl precursors under photoredox catalysis in various transformations.³⁰ The combination of sulfur dioxide and Katritzky salts was reported as well. Wu and co-workers developed the first example by using Katritzky salts as alkyl radical precursors in the reaction of potassium metabisulfite and silyl enol ethers under photoredox catalysis, leading to diverse dialkyl sulfones (Scheme 15).³¹ A broad reaction scope was demonstrated and various functional groups were all tolerated including amino, cyano, hydroxy, and trifluoromethyl groups. This transformation proceeds efficiently under mild conditions in the presence of a photocatalyst and visible



Scheme 15 Reactions of Katritzky salts, potassium metabisulfite and silyl enol ethers under photoredox catalysis.

light irradiation, giving rise to the corresponding dialkyl sulfones in good yields. A photoinduced radical pathway under visible-light conditions was proposed. The experimental results showed that an alkyl radical generated *in situ* from the Katritzky salt *via* reductive single electron transfer by visible-light excited Ir(III) species would initiate the reaction. After combination of sulfur dioxide from potassium metabisulfite, the alkylsulfonyl radical would be produced, which would be trapped by silyl enol ether, leading to a carbon radical intermediate. In the presence of Ir(IV), this carbon radical intermediate would be oxidized to carbocation species, which would then undergo desilylation assisted by a base to afford the corresponding β -keto sulfone.

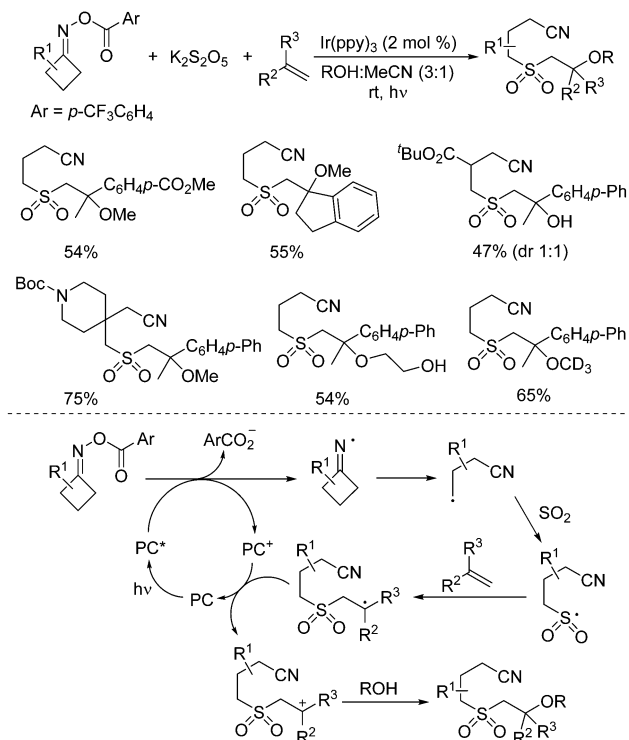
4-Substituted Hantzsch esters as alkyl radical reservoirs have been demonstrated, and the alkyl units from 4-substituted Hantzsch esters could be easily introduced into various small molecules.³² In the presence of a photoredox catalyst under visible light irradiation, alkyl radicals would be generated from 4-alkyl Hantzsch esters through single electron transfer (SET). Thus, synthesis of alkynyl sulfones through a reaction of 4-alkyl Hantzsch esters, sodium metabisulfite, and alkynyl bromides under metal-free photoinduced conditions was accomplished (Scheme 16).³³ This transformation proceeds smoothly under visible light irradiation at room temperature, giving rise to the corresponding alkylalkynyl sulfones in moderate to good yields. The control experiments showed that the alkyl radical generated *in situ* from 4-alkyl Hantzsch esters in the presence of the photocatalyst would initiate the reaction. After capture of sulfur



Scheme 16 Synthesis of alkynyl sulfones through a reaction of 4-alkyl Hantzsch esters, sodium metabisulfite, and alkynyl bromides under metal-free photoinduced conditions.

dioxide from sodium metabisulfite, the alkylsulfonyl radical would be formed, which would attack the triple bond of alkynyl bromide leading to a vinyl radical intermediate. Single electron transfer would then occur with the assistance of the excited photocatalyst to produce a vinyl anion, which would afford the corresponding alkylalkynyl sulfone with the release of a bromide anion.

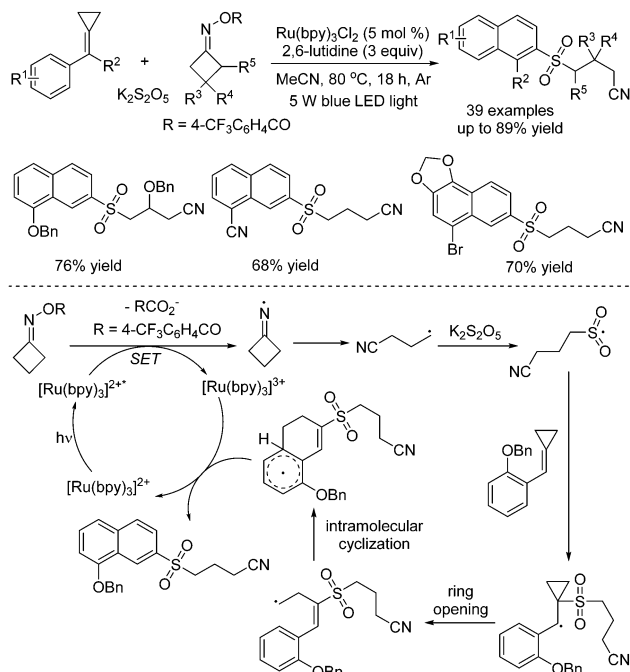
So far, much focus has been centered on the reactions of iminyl radicals. In some cases, iminyl radicals could be easily formed *via* a photoreductive strategy from *O*-acyl oximes under visible light irradiation.³⁴ A photoredox-catalyzed multicomponent reaction of *O*-acyl oximes, potassium metabisulfite, alkenes, and nucleophiles under visible light irradiation is developed (Scheme 17).³⁵ This transformation proceeded through sulfonylation of *O*-acyl oximes *via* iminyl radicals with the insertion of sulfur dioxide. The nucleophiles included alcohols and water. A range of β -alkoxy sulfones and β -hydroxyl sulfones was obtained in moderate to good yields with good functional group compatibility. Primary alcohols were effective in this transformation. However, the reactions of secondary alcohols and tertiary alcohols gave inferior results. Reaction in methan-*d*₃-*ol-d* instead of methanol was workable as well. β -Hydroxy sulfones could be prepared when the reactions took place in a mixture of water and MeCN. Additionally, this photoredox-catalyzed multicomponent reaction showed excellent chemoselectivity during the reaction process. Mechanistic studies were performed, which showed that the reaction was initiated by the iminyl radical formed *in situ* from *O*-acyl oxime *via* N–O bond dissociation under visible light irradiation in the presence of the photocatalyst. Then, the intramolecular C–C bond cleavage of the iminyl radical would



Scheme 17 Photoredox-catalyzed reaction of *O*-acyl oximes, potassium metabisulfite, alkenes, and nucleophiles under visible light irradiation.

occur to provide a carbon radical, which would react with sulfur dioxide from potassium metabisulfite, leading to a sulfonyl radical intermediate. Subsequently, the sulfonyl radical would attack the double bond of alkene giving rise to another carbon radical intermediate, which would then undergo oxidative single electron transfer *via* the oxidized form of the photocatalyst to produce the corresponding cation intermediate. With the assistance of a base, the alcohol or water would act as the nucleophile to attack the cation intermediate, affording the expected β -alkoxy sulfone and β -hydroxyl sulfone.

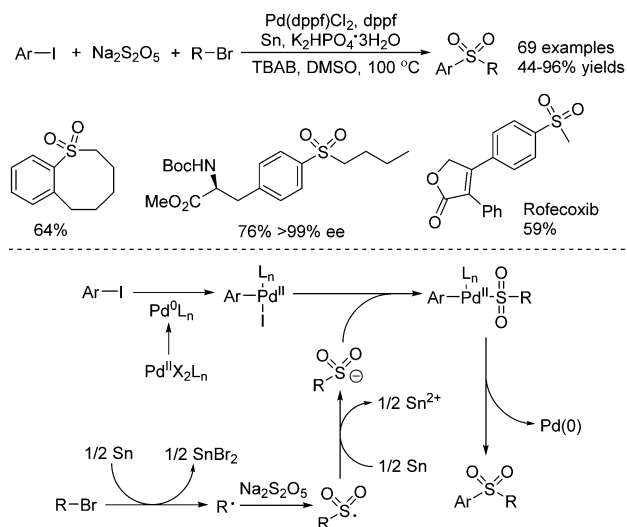
Tang and co-workers described the synthesis of 2-cyanoalkyl-sulfonated 3,4-dihydro-naphthalenes *via* visible-light photoredox-catalyzed dual carbon-carbon bond cleavage of methylenecyclopropanes, potassium metabisulfite and cycloketone oximes (Scheme 18).³⁶ Compared with the above method as reported by Wu,³⁵ methylenecyclopropanes were used as a replacement for alkenes. For the mechanism, similar to Wu's report, the iminyl radical formed *in situ* from *O*-acyl oxime *via* N-O bond dissociation under visible light irradiation in the presence of the photocatalyst would initiate the reaction. Then, the intramolecular C-C bond cleavage of the iminyl radical would take place to provide a carbon radical, which would react with sulfur dioxide from potassium metabisulfite, giving rise to a sulfonyl radical intermediate. This sulfonyl radical intermediate would attack the C=C double bond of methylenecyclopropane, leading to a carbon radical intermediate. Subsequently, ring-opening of cyclopropane would occur with another carbon-carbon bond cleavage. Following intramolecular cyclization and oxidative single electron transfer assisted by the photocatalyst, the final product would be obtained.



Scheme 18 Photoredox-catalyzed reaction of potassium metabisulfite, methylenecyclopropanes and cycloketone oximes.

A metal-free three-component reaction of aryl/alkyl iodides, sulfur dioxide and 3-azido-2-methylbut-3-en-2-ol under ultraviolet irradiation at room temperature is developed, leading to 2-(arylsulfonyl)acetonitriles in moderate to good yields.³⁷ Various functional groups are compatible including amino, ester, halo, and trifluoromethyl groups. Although DABCO-(SO₂)₂ was used as the source of sulfur dioxide, the reaction using potassium metabisulfite or sodium metabisulfite was also effective with lower yields. The aryl radical generated *in situ* from aryl iodide under ultraviolet irradiation initiated the reaction, which underwent sulfonylation with sulfur dioxide, leading to an arylsulfonyl radical intermediate.

Jiang and co-workers described the synthesis of sulfones through a palladium-catalyzed three-component reductive cross-coupling reaction of sodium metabisulfite, aryl iodides, and alkyl halides (Scheme 19).³⁸ Although this transformation proceeded in the presence of tin at high temperature, some biomolecules including steroids, saccharides, and amino acids were all compatible under the conditions. Intramolecular cyclic sulfones were prepared as well from five- to twelve-membered rings. Additionally, four drug molecules bearing functional groups were obtained *via* late-stage sulfur dioxide insertion. From mechanistic studies, it was shown that an alkyl radical would be formed from the combination of alkyl bromide with tin *via* a single-electron transfer process. This alkyl radical would be trapped by sodium metabisulfite, leading to an alkylsulfonyl radical intermediate, which would be reduced by tin, affording the alkylsulfonyl anion. In the meantime, the oxidative addition of aryl iodide to Pd(0) would provide Pd(II) species, which would react with the alkylsulfonyl anion leading to another Pd(II) complex. Further reductive elimination from this Pd(II) complex would produce the desired sulfone with the release of the Pd(0) catalyst.



Scheme 19 A palladium-catalyzed three-component reductive cross-coupling reaction of sodium metabisulfite, aryl iodides, and alkyl halides.

5. Conclusions and outlook

In this updated report, the recent advances in sulfonylation reactions using potassium/sodium metabisulfite as the source of sulfur dioxide from Dec. 2018 are summarized. In this field, method development by using potassium/sodium metabisulfite in sulfonylation reactions boomed last year. As mentioned above, these approaches are attractive and promising, since potassium/sodium metabisulfite is abundant, easily available and cheap. Diverse sulfonyl compounds including sulfones and sulfonamides can be accessed easily and conveniently. In most cases, the transformations go through radical processes with the insertion of sulfur dioxide under mild conditions. Additionally, transition metal catalysis is applied in the reactions for the synthesis of sulfonyl-containing compounds. Among the approaches, photo-induced conversions under visible light or ultraviolet irradiation are also involved.

However, some challenges are still to be explored. Since many marketed drugs are chiral molecules, asymmetric synthesis of sulfonyl-containing compounds through enantioselective reactions of potassium/sodium metabisulfite will be the focus in the near future, which has not been disclosed yet. Additionally, examples are rare of using potassium/sodium metabisulfite as the source of sulfur dioxide for the preparation of sulfonyl-containing drugs, although the developed methods have been employed successfully for the late-stage modification of currently marketed drugs. Thus, more efficient methods using potassium/sodium metabisulfite in organic synthesis will continuously appear, and the application of these methods for the synthesis of drugs, especially chiral sulfonyl-containing drugs, is anticipated.

Conflicts of interest

There are no conflicts to declare.

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