

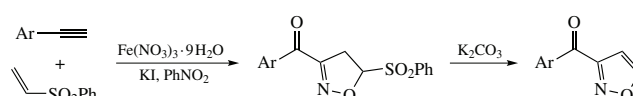
One-pot synthesis of 5-phenylsulfonyl-3-arylisoxazolines and 3-arylisoxazoles from alkynes and (phenylsulfonyl)ethene

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Iron(III) nitrate-assisted cycloaddition of (phenylsulfonyl)ethene to arylacetylenes in the presence of KI affords 5-phenylsulfonyl-3-arylisoxazolines whose treatment with K_2CO_3 provides 4,5-unsubstituted 3-arylisoxazoles. Both synthetic steps can be performed in a one-pot manner.



Keywords: iron nitrate, nitration, alkynes, 1,3-dipolar cycloaddition, isoxazolines, isoxazoles.

Isoxazoline and isoxazole derivatives are very useful compounds that display attractive biological and pharmaceutical activities.^{1–6} They are also utilized as efficient chiral ligands⁷ and building blocks in organic synthesis.^{8–11} Generally, the 1,3-dipolar cycloaddition of nitrile oxides to alkenes or alkynes is the most straightforward access to these compounds.¹² In this context, oximes,¹³ nitro alkanes,¹⁴ ketones,^{15,16} primary amines¹⁷ and diazo compounds¹⁸ have been employed as nitrile oxide precursors. However, some of the reported procedures suffered from harsh reaction conditions, limited substrate scope or required the application of the substrates as the solvents.

The use of alkynes as nitrile oxide precursors in the presence of a nitration and cyclization reagent have attracted much attention due to their easy accessibility and high reactivity.^{19–22} Recently, iron and copper nitrates have been successfully employed in the annulation of two different alkynes^{23,24} and 1,3-dipolar cycloaddition of alkynes with alkenes²⁵ or nitriles.²⁶ Inspired by these contributions, we herein report the iron nitrate-mediated synthesis of 5-phenylsulfonyl-3-arylisoxazolines from alkynes. It is worth noting that the further desulfonylation/aromatization of phenylsulfonyl-3-arylisoxazolines can provide 4,5-unsubstituted 3-arylisoxazoles. To the best of our knowledge, the synthesis of 4,5-unsubstituted 3-arylisoxazoles is still less exploited up to date.²⁷

Initially, we started to optimize the 1,3-dipolar cycloaddition of phenylacetylene **1a** and (phenylsulfonyl)ethene **2** as the model substrates (Table 1). Firstly, different additives were screened, and KI was the best choice (entries 1–4). In the absence of KI, the yield decreased significantly. Previous reports^{25,26} showed that Bu^tCN served as a good ligand in iron nitrate-mediated nitration reactions. However, in our experiments only moderate yield was achieved (entry 4). Screening of solvents showed that nitrobenzene was superior to toluene, THF, acetonitrile and DMF (entries 2 and 5–8). Slightly lower yields were obtained when the reaction was performed either at 80 or 120 °C (entries 10 and 11). Switching the nitration reagent to Ce(NH₄)₂(NO₃)₆ or Bu^tONO gave rather poor results (entries 12 and 13). The reaction was also influenced by loading amounts of

Fe(NO₃)₃·9H₂O or KI, namely, 2 equiv. of Fe(NO₃)₃·9H₂O and 1 equiv. of KI were optimal (entry 14). In addition, an inert atmosphere would benefit this reaction since the Glaser coupling reaction could be avoided (entry 15).

A series of alkynes was then tested under the optimized reaction conditions (Scheme 1).[†] Aromatic alkynes **1a–k** with various functional groups showed good reactivities, affording the corresponding products **3a–k** in moderate to good yields. Steric hindrance showed little influence on the reaction. Reaction of 1-ethynyl-naphthalene also proceeded well, giving product **3l** in 74% yield. 2-Ethynylthiophene also was transformed into derivative **3m** in 53% yield. Unfortunately, with aliphatic pent-1-yne only trace amounts of the product was formed.

Compounds of type **3** can possess promising properties. For example, the phenylsulfonyl group can be selectively reduced, enabling the access to isoxazolines bearing phenylthio substituent. Also, this function can serve as a leaving group. In this work, heating of representative compounds **3a–c** with catalytic amount of K₂CO₃ provided 4,5-unsubstituted 3-arylisoxazoles **4a–c** (see Scheme 1). This elimination can be

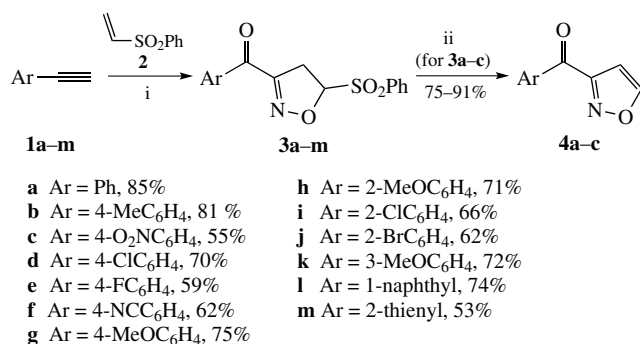
[†] General procedure for the synthesis of **3** and **4**. A sealed tube equipped with a magnetic stirrer bar was charged with alkyne **1a–m** (0.3 mmol), sulfonylthene **2** (0.6 mmol, 2.0 equiv.), Fe(NO₃)₃·9H₂O (0.6 mmol, 2.0 equiv.), KI (0.3 mmol, 1.0 equiv.) and PhNO₂ (2 ml) under N₂. The mixture was then heated to 100 °C and stirred for 12 h. Upon the reaction completion, the resulting solution was quenched with saturated aqueous Na₂S₂O₃. The collected organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using light petroleum/ethyl acetate as eluent to afford products **3a–m**.

When the 1,3-dipolar cycloaddition was complete, K₂CO₃ (0.03 mmol, 0.1 equiv.) was added, and the mixture was stirred at 100 °C for more 6 h. The mixture was cooled and extracted with EtOAc (3×10 ml). The collected organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using light petroleum/ethyl acetate as eluent to afford products **4**.

Table 1 Optimization of iron(III) nitrate-assisted cycloaddition of phenylacetylene **1a** to (phenylsulfonyl)ethene **2**.^a

Entry	Nitration reagent	Additive	Solvent	<i>T</i> /°C	Yield of 3a (%) ^b
1	Fe(NO ₃) ₃ ·9H ₂ O	–	PhNO ₂	100	39
2	Fe(NO ₃) ₃ ·9H ₂ O	KI	PhNO ₂	100	85
3	Fe(NO ₃) ₃ ·9H ₂ O	I ₂	PhNO ₂	100	70
4	Fe(NO ₃) ₃ ·9H ₂ O	Bu ^c CN	PhNO ₂	100	62
5	Fe(NO ₃) ₃ ·9H ₂ O	KI	Toluene	100	51
6	Fe(NO ₃) ₃ ·9H ₂ O	KI	THF	65	59
7	Fe(NO ₃) ₃ ·9H ₂ O	KI	MeCN	80	46
8	Fe(NO ₃) ₃ ·9H ₂ O	KI	DMF	100	30
9	Fe(NO ₃) ₃ ·9H ₂ O	KI	PhNO ₂	80	75
10	Fe(NO ₃) ₃ ·9H ₂ O	KI	PhNO ₂	120	83
11	Cu(NO ₃) ₂ ·3H ₂ O	KI	PhNO ₂	100	74
12	Ce(NH ₄) ₂ (NO ₃) ₆	KI	PhNO ₂	100	20
13	Bu ^c ONO	KI	PhNO ₂	100	0
14	Fe(NO ₃) ₃ ·9H ₂ O	KI	PhNO ₂	100	48, ^c 85 ^d
15	Fe(NO ₃) ₃ ·9H ₂ O	KI	PhNO ₂	100	53, ^e 84, ^f 70 ^g

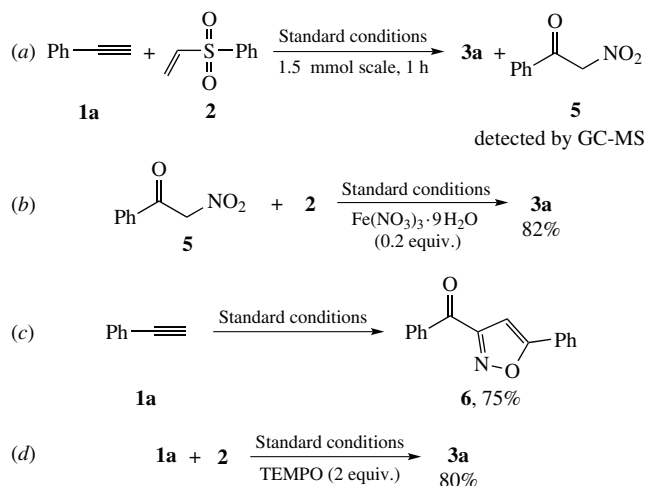
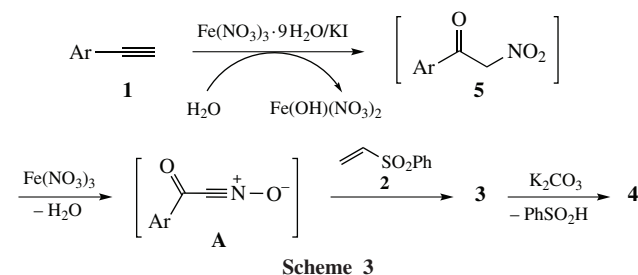
^aReaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol, 2.0 equiv.), nitration reagent (0.6 mmol, 2.0 equiv.), additive (0.3 mmol, 1.0 equiv.), solvent (2 ml), heating under nitrogen atmosphere, 12 h. ^bIsolated yield. ^cFe(NO₃)₃·9H₂O (1.0 equiv.). ^dFe(NO₃)₃·9H₂O (3.0 equiv.). ^eKI (0.5 equiv.). ^fKI (1.5 equiv.). ^gUnder air.

**Scheme 1** Reagents and optimized conditions: i, **1** (0.3 mmol), **2** (0.6 mmol), Fe(NO₃)₃·9H₂O (0.6 mmol), KI (0.3 mmol), PhNO₂ (2 ml), N₂, 100 °C, 12 h; ii, K₂CO₃ (0.1 equiv.), 100 °C, 6 h.

also promoted by some other bases and even acids (for details, see Table S1 of Online Supplementary Materials, and cf. ref. 27).

Some control experiments were performed to gain insight into the mechanism. Initially, the formation of α -nitroacetophenone **5** was detected by GC-MS in scale-up experiment [Scheme 2, equation (a)]. When compound **5** was employed as the substrate, product **3a** was obtained in 82% yield even with catalytic amount of Fe(NO₃)₃·9H₂O [equation (b)]. These results suggested that compound **5** may be the real active intermediate in this reaction. Next, processing of **1a** in the absence of sulfonylethene **2** gave product **6** in 75% yield, indicating that the reaction was initiated from **1a** [equation (c)]. Finally, no suppression effect was observed when 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) was added, testifying that a radical mechanism could be ruled out [equation (d)].

A mechanism was proposed based on the control experiments and the literature^{24,26} data (Scheme 3). Initially, alkyne **1** is transformed into nitro ketone **5** in the presence of Fe(NO₃)₃.^{24,25} Lai and co-workers demonstrated that the addition of KI would make this transformation to proceed easier.²⁴ Then Fe(NO₃)₃-assisted dehydration occurs to afford nitrile oxide **A**. Intermediate **A** and **2** undergo 1,3-dipolar cycloaddition to give product **3**. Finally, potassium carbonate causes removal of benzenesulfinic acid from **3** affording the aromatized product **4**.²⁷

**Scheme 2****Scheme 3**

In summary, we have developed an iron(III) nitrate-assisted synthesis of 5-phenylsulfonyl-3-arylisoaxazolines from alkynes. In this process, alkynes serve as nitrile oxide precursors, iron(III) nitrate acts as the nitration and cyclization reagent, and KI is used as an effective additive. Aromatic alkynes showed good reactivities, in contrast to aliphatic alkynes. Final removal of benzenesulfinic acid with K₂CO₃ provides 4,5-unsubstituted 3-arylisoaxazoles.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.036.

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