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One-pot synthesis of 5-phenylsulfonyl-3-aroylisoxazolines and 3-aroylisoxazoles from alkynes and (phenylsulfonyl)ethene

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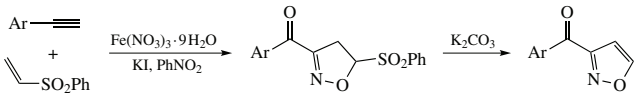
Iron(III) nitrate-assisted cycloaddition of (phenylsulfonyl)-ethene to arylacetylenes in the presence of KI affords 5-phenylsulfonyl-3-aroylisoxazolines whose treatment with K_2CO_3 provides 4,5-unsubstituted 3-aroylisoxazoles. Both synthetic steps can be performed in a one-pot manner.



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Isoxazoline and isoxazole derivatives are very useful compounds that display attractive biological and pharmaceutical activities.[1–6] They are also utilized as efficient chiral ligands[7] 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 amines[17] and diazo compounds[18] 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 alkenes[25] or nitriles.[26] Inspired by these contributions, we herein report the iron nitrate-mediated synthesis of 5-phenylsulfonyl-3-aroylisoxazolines from alkynes. It is worth noting that the further desulfonylation/aromatization of phenylsulfonyl-3-aroylisoxazolines can provide 4,5-unsubstituted 3-aroylisoxazoles. To the best of our knowledge, the synthesis of 4,5-unsubstituted 3-aroylisoxazoles 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 $Ce(NH_4)_2(NO_3)_6$ or Bu^tONO gave rather poor results (entries 12 and 13). The reaction was also influenced by loading amounts of $Fe(NO_3)_3 \cdot 9H_2O$ or KI, namely, 2 equiv. of $Fe(NO_3)_3 \cdot 9H_2O$ 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-ethynylnaphthalene 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 K_2CO_3 provided 4,5-unsubstituted 3-aroylisoxazoles **4a**–**c** (see Scheme 1). This elimination can be

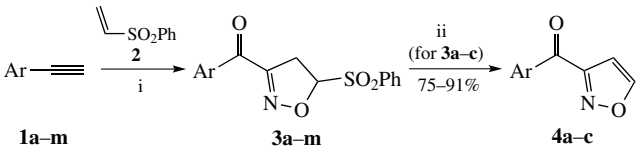
† *General procedure for the synthesis of* **3** and **4**. A sealed tube equipped with a magnetic stirrer bar was charged with alkyne **1a**–**m** (0.3 mmol), sulfonylethene **2** (0.6 mmol, 2.0 equiv.), $Fe(NO_3)_3 \cdot 9H_2O$ (0.6 mmol, 2.0 equiv.), KI (0.3 mmol, 1.0 equiv.) and $PhNO_2$ (2 ml) under N_2. 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 $Na_2S_2O_3$. The collected organic extracts were dried over Na_2SO_4. 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, K_2CO_3 (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 Na_2SO_4. 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	*T*/°C	Yield of **3a** (%)[b]
1	$Fe(NO_3)_3 \cdot 9H_2O$	–	$PhNO_2$	100	39
2	$Fe(NO_3)_3 \cdot 9H_2O$	KI	$PhNO_2$	100	85
3	$Fe(NO_3)_3 \cdot 9H_2O$	I_2	$PhNO_2$	100	70
4	$Fe(NO_3)_3 \cdot 9H_2O$	Bu^tCN	$PhNO_2$	100	62
5	$Fe(NO_3)_3 \cdot 9H_2O$	KI	Toluene	100	51
6	$Fe(NO_3)_3 \cdot 9H_2O$	KI	THF	65	59
7	$Fe(NO_3)_3 \cdot 9H_2O$	KI	MeCN	80	46
8	$Fe(NO_3)_3 \cdot 9H_2O$	KI	DMF	100	30
9	$Fe(NO_3)_3 \cdot 9H_2O$	KI	$PhNO_2$	80	75
10	$Fe(NO_3)_3 \cdot 9H_2O$	KI	$PhNO_2$	120	83
11	$Cu(NO_3)_2 \cdot 3H_2O$	KI	$PhNO_2$	100	74
12	$Ce(NH_4)_2(NO_3)_6$	KI	$PhNO_2$	100	20
13	Bu^tONO	KI	$PhNO_2$	100	0
14	$Fe(NO_3)_3 \cdot 9H_2O$	KI	$PhNO_2$	100	48,[c] 85[d]
15	$Fe(NO_3)_3 \cdot 9H_2O$	KI	$PhNO_2$	100	53,[e] 84,[f] 70[g]

[a] Reaction 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. [b] Isolated yield. [c] $Fe(NO_3)_3 \cdot 9H_2O$ (1.0 equiv.). [d] $Fe(NO_3)_3 \cdot 9H_2O$ (3.0 equiv.). [e] KI (0.5 equiv.). [f] KI (1.5 equiv.). [g] Under air.



1a–m **3a–m** **4a–c**

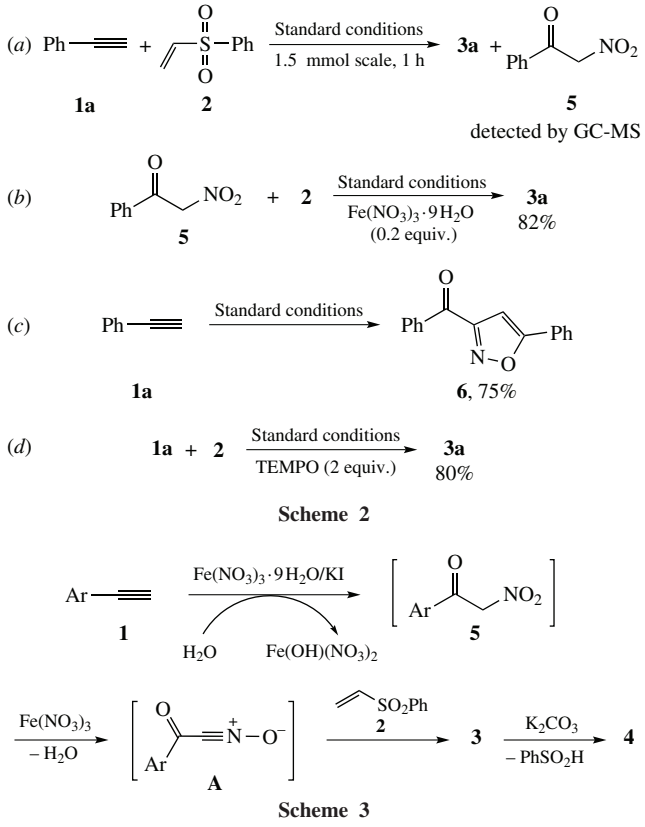
a Ar = Ph, 85%
b Ar = 4-MeC_6H_4, 81 %
c Ar = 4-$O_2NC_6H_4$, 55%
d Ar = 4-ClC_6H_4, 70%
e Ar = 4-FC_6H_4, 59%
f Ar = 4-NCC_6H_4, 62%
g Ar = 4-$MeOC_6H_4$, 75%
h Ar = 2-$MeOC_6H_4$, 71%
i Ar = 2-ClC_6H_4, 66%
j Ar = 2-BrC_6H_4, 62%
k Ar = 3-$MeOC_6H_4$, 72%
l Ar = 1-naphthyl, 74%
m Ar = 2-thienyl, 53%

Scheme 1 *Reagents and optimized conditions*: i, **1** (0.3 mmol), **2** (0.6 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (0.6 mmol), KI (0.3 mmol), $PhNO_2$ (2 ml), N_2, 100 °C, 12 h; ii, K_2CO_3 (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 $Fe(NO_3)_3 \cdot 9H_2O$ [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-tetramethylpiperidinyl-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 $Fe(NO_3)_3$.[24,25] Lai and co-workers demonstrated that the addition of KI would make this transformation to proceed easier.[24] Then $Fe(NO_3)_3$-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-aroylisoxazolines 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 K_2CO_3 provides 4,5-unsubstituted 3-aroylisoxazoles.

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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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