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ARTICLE TYPE

Silver-catalyzed direct spirocyclization of alkynes with thiophenols: a simple and facile approach to 3-thioazaspiro[4,5]trienones†

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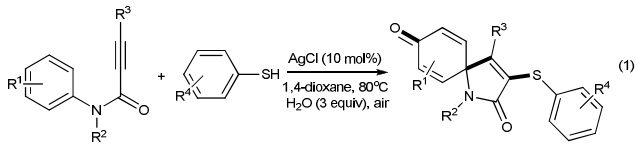
A new and convenient silver-catalyzed direct oxidative spirocyclization of alkynes with thiophenols is described. This methodology provides a simple and practical approach to various 3-thioazaspiro[4,5]trienones in moderate to good yields with high atom efficiency and excellent functional group tolerance.

As a highly important class of compounds, sulfur-containing molecules exhibited a wide range of applications in organic synthesis,[1,2] medicinal chemistry,[3] and materials science.[4] Consequently, numerous efforts has been made to explore new efficient methods for introduction of the sulfur group into organic molecules in the synthetic community. Among many of the synthetic transformations, the difunctionalization of C-C unsaturated bonds with thiolation agents has recently attracted great interests of chemists due to it could provide rapid and concise access to various sulfur-containing compounds.[5-10] Over the past decades, many transition-metal-catalyzed or metal-free difunctionalizations of alkenes for constructing sulfur-containing compounds have been developed,[5-8] such as alkoxythiolation,[5] hydroxythiolation,[6] acetoxythiolation,[7] and sulfamination.[8] Nevertheless, to date, only a few strategies for the fabrication of sulfur compounds has been exploited through the difunctionalization of alkynes.[9,10] Recently, Li et al. reported $Mn(OAc)_2$-catalyzed difunctionalization of alkynes with thiophenols leading to benzothiophenes.[10a] Zou and co-workers reported oxidative radical oxythiolation of alkynes with thiophenols to access α-thioaldehydes.[10b] Yi also described iodothiolation of alkynes with sodium arenesulfinates for the construction of β-iodoalkenyl sulfides under metal-free conditions.[10c] Although some remarkable progress has been made in this field, the development of new, convenient, efficient and atom-economical protocols through difunctionalization of alkynes to assembly structurally diverse and complex sulfur-containing chemical frameworks still remains a highly desirable but challenging task in the modern organic chemistry.

As part of our continued interest in the difunctionalization of alkynes,[11] we herein report a new silver-catalyzed oxidative spirocyclization of N-arylpropiolamides with thiophenols leading to 3-thioazaspiro[4,5]trienones (eqn (1)). Azaspiro[4,5]trienone is the common core structure in many natural products and pharmaceuticals as well as a versatile building block in organic synthesis.[12,13] Recently, several strategies based on the difunctionalization of alkynes has been applied successfully for the construction of various functionalized azaspiro[4,5]trienones.[11a,14] Through this methodology, some additional functional groups could be introduced into the azaspiro[4,5]trienone framework. Very recently, a report on the use of the reagent combination of N-(*p*-methoxyaryl)propiolamides, disulfides, $CuCl_2$, O_2, and H_2O in DMF at 100°C for the synthesis of 3-thioazaspiro[4,5]trienones was disclosed by Li and Song.[15] However, this method is restricted with the use of the preformed disulfides and arylalkynes bearing the *para*-methoxy substituent on the aryl ring. Moreover, the mechanism for the *ipso*-cyclization method was not studied in detail.

The present protocol offer a convenient and efficient route to a series of biologically important 3-thioazaspiro[4,5]trienones via direct silver-catalyzed *ipso*-cyclization of *para*-unsubstituted arylalkynes with commercial available thiophenols, in which the C-S, C-C, and C=O bonds can be sequential formed in a single operation (eqn (1)). Preliminary mechanistic studies suggested that the carbonyl oxygen atom of 3-thioazaspiro[4,5]trienones originated from the water and this reaction might involve a radical process.



(1)

In our initial studies, the reaction of N-methyl-N,3-diphenylpropiolamide **1a** with 4-methylbenzenethiol **2a** was performed to examine the catalytic activity of various catalysts including Cu, Pd, Ni, Fe, Ag, and inodized salts in the presence of H_2O (3 equiv) in CH_3CN under air. As shown in Table 1, among those catalysts tested (Table 1, entries 1-11), silver salts especially AgCl was found to be the best catalyst to catalyze the formation of product **3a** (Table 1, entry 8). Among the solvents examined, 1,4-dioxane was demonstrated to be more effective

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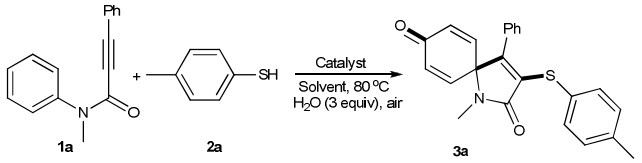
Table 1 Optimization of the reaction conditions[a]



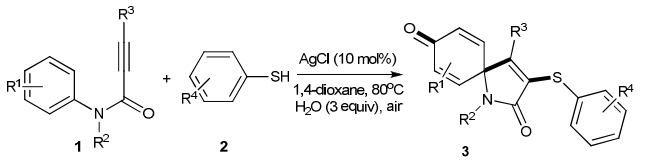
Entry	Catalyst	Solvent	Yield(%)[b]
1	CuI	CH_3CN	<10
2	$Pd(OAc)_2$	CH_3CN	30
3	$NiCl_2$	CH_3CN	33
4	$FeCl_3.6H_2O$	CH_3CN	<10
5	Ag_2O	CH_3CN	24
6	AgOAc	CH_3CN	42
7	Ag_2CO_3	CH_3CN	<10
8	AgCl	CH_3CN	67
9	$AgNO_3$	CH_3CN	65
10	KI	CH_3CN	23
11	TBAI	CH_3CN	28
12	AgCl	1,4-dioxane	76
13	AgCl	DME	65
14	AgCl	DCE	64
15	AgCl	THF	40
16	AgCl	Toluene	68
17	AgCl	DMF	42
18	AgCl	DMSO	36
19	AgCl	1,4-dioxane	58[c]
20	AgCl	1,4-dioxane	46[d]
21	AgCl	1,4-dioxane	14[e]
22	AgCl	1,4-dioxane	66[f]
23	AgCl	1,4-dioxane	69[g]

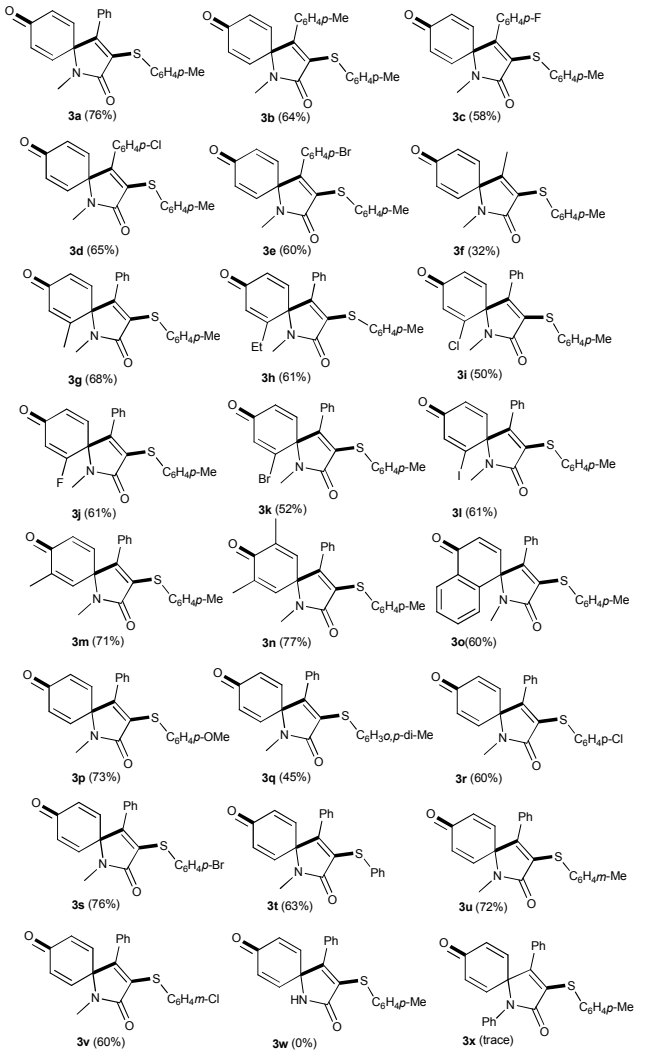
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst (10 mol%), H_2O (3 equiv), anhydrous solvent (2 mL), 80°C, 14 h, air. DCE: 1,2-dichloroethane; DME: 1,2-Dimethoxyethane. [b] Isolated yields based on **1a**. [c] AgCl (5 mol%), [d] AgCl (2 mol%), [e] 25°C, [f] 60 °C, [g] 100°C.

than the others such as CH_3CN, DME, DCE, THF, toluene, DMF, and DMSO (Table 1, entries 8, 12-18). In addition, the reaction efficiency was obviously low with the decreasing of AgCl loading (Table 1, entries 19-20). We found that the reaction temperature played an important role in this reaction (Table 1, entries 12, 21-23). The desired product was obtained in only 14% yield when the model reaction was carried out at room temperature (Table 1, entry 21), and the reaction at 80°C gave the best results. After a series of detailed investigations, the best yield of **3a** (76%) was obtained by employing **1a** (0.25 mmol), 2a (0.5 mmol), AgCl (10 mol%), and H_2O (3 equiv) in 1,4-dioxane at 80°C (Table 1, entry 12).

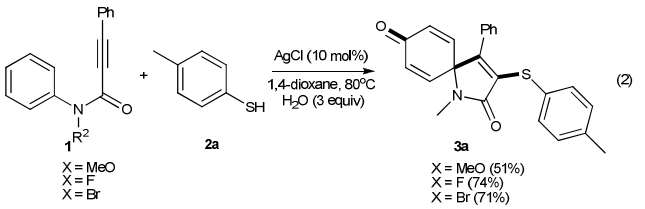
Upon optimization of the reaction conditions, the scope of this new spirocyclization reaction was evaluated, with some results summarized in Table 2. Firstly, the effects of the substituent on the alkynyl moiety were investigated. Arylalkynes bearing both of the electron-donating and electron-withdrawing groups on the aromatic moieties were tolerated in this reaction to give the corresponding products in good yields (**3a**-**3e**). As expected, alkylalkyne was also suitable for this reaction, but leading to the desired product in the relatively lower yield (**3f**). Subsequently, N-arylpropiolamides with various substitution patterns at the aniline moieties were examined. The *ortho*- or *meta*-position of the aniline moieties were compatible with this reaction, with the desired products obtained in moderate to good yields (**3g**–**3n**). Notably, various halogen groups were consistent with the optimized conditions, thereby facilitating further transformations

Table 2 Results for the reaction of the spirocyclization of alkynes with thiophenols [ab]





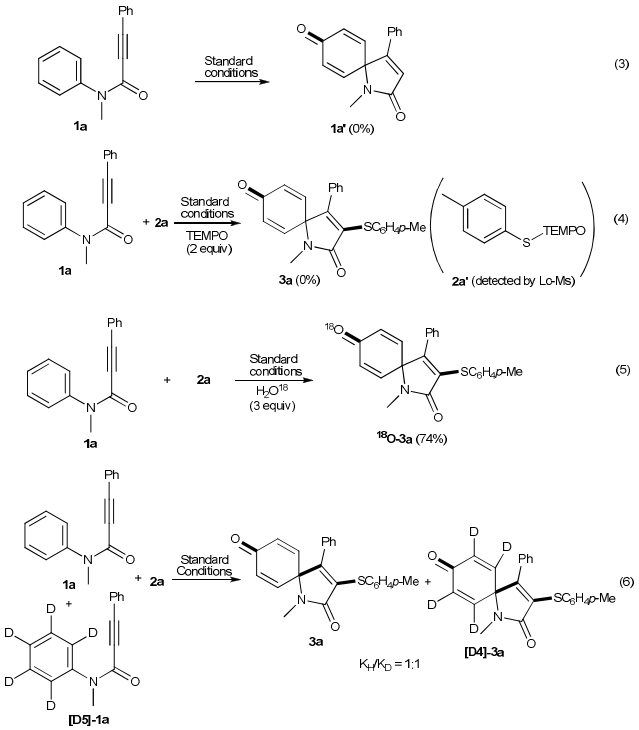
[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), AgCl (10 mol%), H_2O (3 equiv), 1,4-dioxane (2 mL), 10-24h, 80°C, under air. [b] Isolated yields based on **1**.



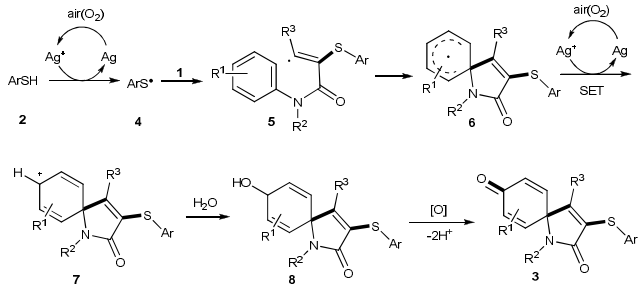
(**3i**–**3l**). Interestingly, the *para*-position substituted N-arylpropiolamides could give the corresponding product **3a** in moderate to good yields by releasing the *para*-substituents (*p*-MeO-, *p*-F, and *p*-Br) (eqn (2)). Meantime, naphthyl moiety could also be used in the reactions to give the expected product

3o in 60% yield. In addition, the reaction could also proceed well by using various thiophenols with an electron-donating group (Me or MeO) or an electron-withdrawing group (Cl or Br) on the aromatic ring to give the corresponding products in moderate to good yields (**3p**–**3v**). Nevertheless, none of the desired product was obtained when changing the N-Me group to the N-H or N-Ph group (**3w** and **3x**), which might be caused by the electronic effect.

Several control experiments were conducted to obtain some insights into this reaction (eqns. (3-6)). Azaspiro[4,5]trienone **1a'** was not detected when N-methyl-N,3-diphenylpropiolamide **1a** was performed dependently under the standard conditions, indicating that azaspiro[4,5]trienone **1a'** might not be the key intermediate in this reaction (eqn (3)). Furthermore, this reaction was completely inhibited when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well known radical-capturing species) was added into reaction system under the standard condition and TEMPO-trapped complex (*p*-MePhS-Tempo) was detected by Lc-Ms analysis (see ESI.†), which suggested that ArS radical might involve in the present reaction system and this transfomation should proceed through a radical pathway (eqn (4)). Moreover, ^{18}O atom-labelling experiment demonstrated that ^{18}O atom could be incorporated into the corresponding product **3a** when the reaction of **1a** with **2a** was carried out in the presence of $H_2{}^{18}O$ (eqn (5)). This result showed that the oxygen atom of carbonyl group originated from water. In addition, the intermolecular kinetic isotope effect (KIE) experiment were carried out with the deuterium labeled substrates (eqn (6)). No kinetic isotope effects (k_H/k_D = 1.0) was observed, which indicated C–H bond cleavage might not be the rate-determining step that was similar to mechanisms proposed in previous reports.[11a,14]



Based on the above experimental results and previous reports[11a,14-18], a postulated reaction pathway was proposed as shown in Scheme 1. Initially, the thiyl radical **4** was generated from thiophenol **2** in the presence of silver salt under air.[16] Then, the addition of thiyl radical **4** to the triple bond of arylpropiolamide **1** gave vinyl radical **5**. Subsequently, the intramolecular *spiro*-cyclization of vinyl radical **5** with an aryl ring would lead to the formation of the radical intermediate **6**. Next, the corresponding cyclohexadienyl cation **7** was produced from intermediate **6** via a single-electron-transfer process. Finally, the nucleophilic addition of H_2O to cation **7** afforded intermediate **8**,[11a,14i,17] which was further oxidized to form the desired product **3**.[11a,14i,18]



Scheme 1. Postulated reaction pathway.

In conclusion, a simple and efficient protocol has been successfully developed for the construction of 3-thioazaspiro[4,5]trienones via silver-catalyzed oxidative spirocyclization of N-arylpropiolamides with thiophenols. Preliminary mechanistic studies indicated that this reaction might involve a radical process and the carbonyl oxygen atom of 3-thioazaspiro[4,5]trienones originated from the water. This simple reaction system is expected to expand the potential applications of functionalized azaspiro[4,5]trienones in the synthetic and pharmaceutical chemistry.

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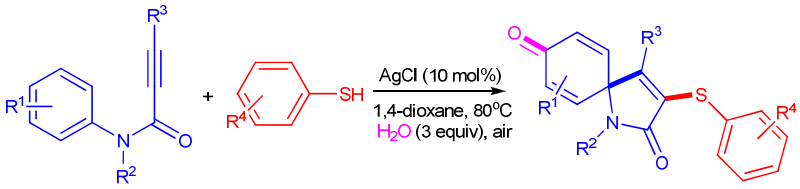

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