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ARTICLE TYPE

Synthesis of 3-Alkyl Spiro[4,5]trienones by Copper-Catalyzed Oxidative *ipso*-Annulation of Activated Alkynes with Unactivated Alkanes

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A Cu-catalyzed oxidative *ipso*-annulation of activated alkynes with unactivated alkanes for the synthesis of 3-alkyl spiro[4,5]trienones is describled. This method allows the formation of two carbon-carbon bonds and one carbon-oxygen bond in a single reaction through a sequence of C-H oxidative coupling, *ispo*-carbocyclization and dearomatization.

Spirocyclohexadienones represent an essential part of the skeleton of numerous natural compounds and pharmaceuticals¹ as well as valuable intermediates in organic synthesis^{1,2} Generally, the spirocyclohexadienone structures are constructed 15 via the oxidative spiro cyclization of phenol derivatives³, transition-metal-catalyzed intramolecular nucleophilic insocarbocyclization of 5-(4-hydroxyaryl)-1-alkenes or 5-(4-hydroxyaryl)-1-alkynes,⁴ and the electrophilic *ipso*-cyclization of 5-(4-methoxyaryl)-1-alkynes.⁵ However, these transformations 20 are restrict to a limited substrate scope, especially the attack functional reagents. Recently, attractive approaches for the synthesis of spirocyclohexadienones via the oxidative radical coupling strategy were developed (Scheme 1a). We have reported radical oxidative *ipso*-carbocyclization of alkynes with aldehydes 25 or ethers for the synthesis of 3-substituted spiro[4,5]trienones (Eqs 1 and 2, Scheme 1).⁸ Very recently, Liu, Liang and coworkers reported copper-catalyzed difunctionalization of activated alkynes leading to 3-trifluoromethly spiro[4,5]trienones via radical oxidation/tandem cyclization/dearomatization



Scheme 1 Oxidative Radical Difunctionalization of Alkynes Leading to Spiro[4,5]trienones.

(Eq 3, Scheme 1).⁹ Although only few approaches have been developed, this strategy would offer a new door for the ³⁵ incorporation of diverse attack functional reagents that extends beyond the existing transformations to access spirocyclohexadienones.

Table 1 Screening of Optimal Conditions^a



Entry	[Cu]	[O] (equiv)	T [°C]	Yield (%) ^b
1	Cu(OAc) ₂ (10)	TBHP (3)	110	57 (82)
2	CuCl ₂ (10)	TBHP (3)	110	30 (80)
3	CuOAc (10)	TBHP (3)	110	22 (76)
4	Cu ₂ O (10)	TBHP (3)	110	28 (59)
5	CuI (10)	TBHP (3)	110	20 (62)
6	$Cu(acac)_2(10)$	TBHP (3)	110	trace
7	$Cu(OAc)_2(10)$	_	110	0
8 ^c	Cu(OAc) ₂ (10)	TBHP (3)	110	8 (81)
9	$Cu(OAc)_{2}$ (10)	DTBP (3)	110	11 (73)
10	$Cu(OAc)_2(10)$	TBPB (3)	110	28 (68)
11	$Cu(OAc)_2(10)$	DCP (3)	110	28 (70)
12	Cu(OAc) ₂ (10)	$K_{2}S_{2}O_{8}(3)$	110	0
13	$Cu(OAc)_2$ (10)	TBHP (2)	110	41 (77)
14	$Cu(OAc)_2(10)$	TBHP (5)	110	53 (81)
15	$Cu(OAc)_2(5)$	TBHP (3)	110	45 (69)
16	Cu(OAc) ₂ (15)	TBHP (3)	110	53 (79)
17	$Cu(OAc)_2$ (10)	TBHP (3)	130	55 (81)
18	$Cu(OAc)_2$ (10)	TBHP (3)	80	23 (87)

^{*a*} Reaction conditions: **1a** (0.2 mmol), [Cu], oxidant and cyclohexane **2a** (1 mL) for 36 h under argon atmosphere. The number in parentheses is the yield based on recovered starting materials. DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide (5M in decane), TBPB = *tert*-⁴⁵ butyl peroxybenzoate, DCP = dicumylperoxide.^{*b*} Isolated yield. ^{*c*} TBHP (70% in water) was added.

Direct C(sp³)-H functionalization for the construction of C-C bonds has emerged as an efficient and straightforward method in modern organic synthesis.⁶ Despite recent efforts, the establishment of general and mild strategies for the engagement ⁵ of unreactived C(sp³)-H bonds in C-C bond forming reactions still remains a formidable challenge.⁷ To the best of our knowledge, approach for the difunctionalization of activated alkynes with unactivated simple alkanes to generate spiro[4,5]trienones has never been reported. Herein, we report a ¹⁰ copper-catalyzed oxidative difunctionalization of activated alkynes with unactivated alkanes to 3-alkyl spiro[4,5]trienones *via* a C-H oxidative radical coupling, *ispo*-carbocyclization and dearomatization tandem process (Eq 4, Scheme 1).

- Our investigation began with oxidative difunctionalization of 1s activated alkynes with unactivated alkanes in the presence of catalytic amount of copper salt and oxidant. (Table 1). In the presence of Cu(OAc)₂ and TBHP, *N*-methyl-*N*,3diphenylpropiolamide **1a** successfully underwent the *ipso*annualtion reaction with cyclohexane **2a**, furnishing the desired 20 3-cyclohexyl-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-
- triene-2,8-dione 3aa in 57% yield (entry 1). Encouraged by these results, a series of other Cu salts, namely CuCl₂, CuOAc, Cu₂O, CuI and Cu(acac)₂ were tested (entries 3-7): all the copper salts showed catalytic activity, but they were less effective than 25 Cu(OAc)₂ (entry 1 vs entries 2-6). It should be noted that no detectable amounts of product 3aa was observed in the absence of oxidant (entry 7). A number of other oxidants, such as TBHP (70% in water) DTBP, TBPB, DCP and K₂S₂O₈, were subsequently examined, and they were less effective than DTBP 30 (entryl vs entries 8-12). Further, K₂S₂O₈ had no effect the reaction (entry 12). Screening on the amount of TBHP and $Cu(OAc)_2$ reaveled that combined 10 mol% of $Cu(OAc)_2$ with 2 equivalents of TBHP gave the best results (entry 1vs entries 13-16). Finally, the effect of reaction temperature were investigated: 35 higher reaction temperature (at 130 °C) did not improve the yield compared with the results at 110 °C (entry 17), but lower temperature (at 80 °C) dramatically reduced the yield (entry 18).

Table 2 Scope of Alkanes $(2)^a$



^{*a*} Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), TBHP (3 equiv, 5 M in decane) and **2** (1 mL) at 110 °C under argon atmosphere for 36 h, isolated yield. The number in parentheses is the yield based on recovered starting materials.

- With the optimal conditions in hand, the substrate scope of this Cu-catalyzed tandem reaction of alkanes 2 with respect to Nmethyl-N,3-diphenylpropiolamide 1a was first investigated (Table 2). In the presence of Cu(OAc)₂ and TBHP, a variety of cycloalkanes, such as methylcyclohexane 1b, cyclopentane 1c, 50 cycloheptane 1d, cyclooctane 1e could successfully reacted with *N*-methyl-*N*,3-diphenylpropiolamide **1a**, allowing easy access to the corresponding products 3ab-ae in moderate yields. For example. the reaction between N-methyl-N.3diphenylpropiolamide 1a and cyclooctane 2e successfully 55 generated product 3ae in 67% yield. Gratifyingly, a straight-chain alkane 2f was found to be viable for the reaction, providing the product 3af in 36% yield. Notably, ethylbenzene 2g was tested under the optimal conditions, affording the corresponding product
- 1-methyl-4-phenyl-3-(1-phenylethyl)-1-azaspiro[4.5]deca-3,6,9-60 triene-2,8-dione **3ag** in 46% yield. Unfortunately, diphenylmethane **2h** was not a suitable substrate more because of the steric effect. Furthermore, toluene derivatives showed good compatibility (Products **3al-ak**).

Table 3 Scope of N-Arylpropiolamides (1)^a





^{*a*} Reaction conditions: **1** (0.2 mmol), Cu(OAc)₂ (10 mol%), TBHP (3 equiv, 5 M in decane) and cyclohexane **2a** (1 mL) at 110 °C under argon atmosphere for 36 h. The number in parentheses is the yield based on ⁷⁰ recovered starting materials.

We next examined the scope of various propiolamides **1** for this oxidative C(sp³)-H functionalization/*ispo*-carbocyclization tandem reaction under the standard reaction conditions. As shown in Table 3, we are pleased to find amides with *N*-Bn or *N*-allyl ⁷⁵ were viable substrates for the reaction (Products **3ba-ca**), but a *N*-H group resulted in no reaction. Subsequently, the substitutes effect of the *N*-aryl moiety was investigated. *N*-Arylpropiolamideswith Me, Ph or OMe groups were welltolerated, affording the corresponding 3-alkyl ⁸⁰ spiro[4,5]trienonesin moderate yields (Products **3ea-ha**). For example, amides **1e** and **1g** with a Me group at the *ortho* or *meta* Published on 23 December 2015. Downloaded by University of Cambridge on 25/12/2015 01:27:44.

position successfully underwent the tandem transformation, furnishing the desired products **3ea** and **3ga** in 48% and 40% yield, respectively. Using naphthalene-derived substrate **1i**, 43% yield of 4'-cyclohexyl-1'-methyl-3'-phenyl-4*H*-spiro[naphthalene-⁵ 1,2'-pyrrole]-4,5'(1'*H*)-dione **3ia** was isolated. Extensive screening revealed that electron-deficient or electron-rich substitutes gropus, including CN, Me, and OMe, on the aromatic ring at the terminal alkyne were tolerated well (Products **3ja-la**). Notably, the amides heteroaryl alkyne **1m** and **1n** reacted with ¹⁰ cyclohexane **2a**, giving the desired products **3ma** and **3ma** in 65% and 38% yield, respectively. Unfortunately, *N*-methyl-*N*phenylbut-2-ynamide **1o** was not suitable substrate for the reaction.

To understand mechanism of the current reaction, a radical ¹⁵ inhibitor, TEMPO (2,2,6,6-tetramethylpiperidinyloxyl), was added to the oxidative C(sp³)-H functionalization/*ispo*carbocyclization reaction (Scheme 2): Adding 2 equiv of TEMPO completely inhibited the conversion of *N*-arylpropiolamides **1a**; However, substrate **2a** was treated with TEMPO to form 1-²⁰ (cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (**4**) in 89% yield (Eq 5 in Scheme 2). It is indicated that the radical process might be involved in this reaction. In addition, treatment of substrate **1a**

- with cyclohexane **2a**, H₂¹⁸O, Cu(OAc)² and TBHP afforded 79.2% ¹⁸O-containing product, which were determined by GC-MS ²⁵ analysis, suggesting that the newly-formed oxygen atom is from
- water (Eq 6 in Scheme 2).



Scheme 2 Control Experiment.

- ³⁰ Based on the above results and previous reports, we proposed a possible mechanism for this system (Scheme 3).⁷⁻⁹ Initially, TBHP readily split into *tert*-butoxy radicals in the presence of Cu(OAc)₂ under heating conditions. Abstraction of a C-H bond in cyclohexane **2a** was subsequently by the *tert*-butoxy radical to ³⁵ yield alkyl radical **A**. Addition of the radical **A** to the C=C bond of *N*-arylpropiolamide **1a** results in the formation of radical intermediate **B**, which upon intramolecular *ipso*-cyclization gives radical intermediate **C**. oxidation of intermediate **C** by the Cu^{III} species forms cation intermediate **D**. Finally, nucleophilic
- $_{40}$ addition and oxidation of intermediate **D** with H₂O and TBHP takes place to afford 3-alkyl spiro[4,5]trienones **3aa**.



Scheme 3 Possible Mechanism.

45 Conclusions

In summary, we have illustrated the first copper-catalyzed C-H oxidative coupling and *ipso*-cyclization of *N*-arylpropiolamides with unactivated alkanes for the synthesis of 3-alkyl spiro[4,5]trienones using TBHP oxidant. This method achieves alkyne difunctionalization through a sequence of C-H oxidative coupling, *ispo*-carbocyclization and dearomatization, and

represents a new shortcut to one-step formation of two C-C bonds and one C-O double bond. Applications of this method in organic synthesis are currently underway in our laboratory.

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