Access to 3-(2-Oxoalkyl)-azaspiro[4.5]trienones *via* Acid-Triggered Oxidative Cascade Reaction through Alkenyl Peroxide Radical Intermediate

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Abstract. Azaspiro[4.5]trienones bearing ketone side chains at the 3-position are prepared from *N*-alkyl-arylpropiolamides and ketones *via* oxidative 1,2-difunctionalization of alkynes. The cascade sequence starts with the generation of alkenyl peroxide intermediates, which are obtained by addition of *tert*-butyl hydroperoxide to ketones in presence of a catalytic amount of a strong acid. Then, the ketone radical adds to alkynes, followed by spirocyclization and dearomatization process. This method represents a new example of difunctionalization of alkynes with simultaneous formation of two carbon–carbon single bonds and one carbon–oxygen double bond in one step.

Keywords: Radical reaction; Cascade; Heterocycles; Ketones; Peroxides

Spirocyclic compounds are important motifs embedded in many natural products, bioactive compounds and functional molecules.^[1] Spiro[4.5]trienones, which are also valuable intermediates in organic synthesis, are often prepared *via* multi-steps synthesis.^[2] One of the most efficient strategy for the construction of multiple bonds in a single operation involves 1,2-difunctionalization of unsaturated molecules,^[3] including photoredox radical process.^[4] Among them oxidative radical-mediated spirocyclization of *N*-arylpropiolamides has proven to be an attractive and straightforward method to access spiro[4.5]trienones in a single step (Scheme 1). For example, radical oxidation of thiols,^[5] sulfonylhydrazides,^[6] diaryl diselenide,^[7] nitrite,^[8] or silanes^[9] gave formation of heteroatom-centered radicals, which added to alkynes followed by spirocyclization and dearomatization (Scheme 1). This procedure allowed the 1,2-difunctionalization of activated alkynes through the one-pot formation of C–heteroatom and C–C single bonds. However, there

are only few reports focusing on the use of carbon-centered radicals, albeit it offers a direct synthesis of polycyclic compounds with the construction of two C–C single bonds. As examples, Liu and Liang have successfully employed Langlois' reagent (CF₃SO₂Na) as trifluoromethyl radical precursor in the synthesis of 3-trifluoromethylated azaspiro[4.5]trienones.^[10] Alkyl radicals –generated by hydrogen abstraction process of ether^[11] or cycloalkane C(sp³)–H bonds^[12] using Cu catalyst with *tert*-butyl hydroperoxide (*t*BuOOH)– have been also employed in those cascade reactions (Scheme 1).

Scheme 1. Previous Syntheses of Functionalized spiro[4.5]trienones *via* Oxidative Radical-Mediated Spirocyclization of *N*-Arylpropiolamides.

In 2014, Klussmann and co-workers reported acid-mediated 1,2-difunctionalization of alkenes with ketones and *tert*-butyl hydroperoxide (*t*BuOOH) (Scheme 2a).^[13] The reaction involves the generation of ketone radical *via* the decomposition of alkenyl peroxide **A** –generated by the addition of *t*BuOOH to

ketone catalyzed by acid— through homolytic bond O–O cleavage.^[14] Independently, Klusmann's and Xia's groups have employed ketone radicals in cascade reaction. Indeed, after addition of ketone radical to alkene unit of *N*-aryl acrylamides, a radical cyclization affords oxindoles in good yields (Scheme 2b).^[15] Xia and coworkers also reported a similar procedure for the preparation of isoquinolinonediones (Scheme 2c).^[16] To the best of our knowledge, alkenyl peroxide intermediates have never been employed in addition of ketone radicals into alkynes, yet. In our continuous efforts to employ carbon-centered radicals in C–H bond functionalizations,^[17] we decided to investigate the reactivity of ketones in presence of *t*BuOOH and activated alkynes such as *N*-arylpropiolamides in order to introduce at least two different functional groups into unsaturated molecules (Scheme 2d).

Scheme 2. Application of Alkenyl Peroxide Intermediates in Organic Synthesis.

We selected *N*-methyl-*N*,3-diphenylpropiolamide and pinacolone as model substrates (Table 1). In the presence of 10 mol% *p*-TsOH and *t*BuOOH (in decane solution) in acetonitrile at 60 °C, 3-(3,3-dimethyl-2-oxobutyl)-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (**1**) is

obtained in a poor yield (entry 1). When the reaction is carried out without acid catalyst or peroxide, no reactions occurred (entries 2 and 3). The presence of oxygen has a deleterious effect on this cascade reaction (entry 4). The use of a larger amount of ketone (10 equiv.) allowed to improve the yield in **1** to 23% (entry 5). A better yield of 52% in **1** is obtained using pinacolone as reactant and solvent (0.2 mol/L) (entry 6). Aqueous solution of *t*BuOOH and other oxidants such as (*t*BuO)₂ or PhI(OAc)₂ are not successful (entries 7-9). *p*-TsOH outperformed other catalyst such as H₂SO₄, AcOH and Cu(OTf)₂ (entries 10-12). A lower catalyst loading resulted in a lower yield, whereas a higher loading of 20 mol% failed to improve the yield (entries 13 and 14). Finally, a prolonged reaction time allowed to improve the yield up to 76% after 48 h (entries 14-16). The structure of **1** has been confirmed by X-ray analysis.^[18] Interestingly, previous method to access azaspiro[4.5]trienones bearing ketone side chains at the 3-position involves oxidative ipso-annulation of specific substrates (i.e. *N*-(*p*-methoxyaryl)propiolamides with α -carbonyl alkyl bromides).^[19]

Table 1. Optimization of the Reaction Conditions

Entry	x	Acid (x)	Solvent	Yield in 1 (%) ^{a)}
1	5 eq	<i>p</i> -TsOH (10)	CH ₃ CN	16
2	5 eq	—	CH ₃ CN	NR
3 ^{b)}	5 eq	<i>p</i> -TsOH (10)	CH ₃ CN	NR
4 ^{c)}	5 eq	<i>p</i> -TsOH (10)	CH ₃ CN	NR
5	10 eq	<i>p</i> -TsOH (10)	CH ₃ CN	23
6	1 mL	<i>p</i> -TsOH (10)	—	52
7 ^{d)}	1 mL	<i>p</i> -TsOH (10)	—	8
8 ^{e)}	1 mL	<i>p</i> -TsOH (10)	—	NR
9 ^{f)}	1 mL	<i>p</i> -TsOH (10)	—	NR
10	1 mL	H ₂ SO ₄ (10)	—	40
11	1 mL	AcOH (10)	—	NR
12	1 mL	Cu(OTf) ₂	—	6
13	1 mL	<i>p</i> -TsOH (5)	—	44
14	1 mL	<i>p</i> -TsOH (20)	—	52
15 ^{g)}	1 mL	<i>p</i> -TsOH (10)	—	68
16 ^{h)}	1 mL	<i>p</i> -TsOH (10)	—	82 (76)

^{a)} Determined by GC-analysis using *n*-dodecane as internal standard and isolated yield was shown in parentheses. ^{b)} Reaction carried out without *t*BuOOH. ^{c)} Reaction carried out under air atmosphere. ^{d)} *t*BuOOH in water solution used instead of *t*BuOOH in decane. ^{e)} (*t*BuO)₂ used instead

of *t*BuOOH in decane. ^{f)} PhI(OAc)₂ used instead of *t*BuOOH in decane. ^{g)} 24 h. ^{h)} 48 h.

With the best conditions in hand, we then studied the effect of the nitrogen substituent on this acid-mediated oxidative radical cascade reaction (Scheme 3). From, non-substituted *N*,3-diphenylpropiolamide, no reaction occurred. The replacement of *N*-methyl by *N*-ethyl substituent has almost no effect as the azaspiro[4.5]trienones **3** is isolated in 79% yield. *N*,3-diphenylpropiolamide bearing a removal *N*-protecting group, e. g., *N*-allyl or *N*-benzyl, also reacted with pinacolone to give the corresponding 3-(3,3-dimethyl-2-oxobutyl)-azaspiro[4.5]trienones **4** and **5** in 53% and 71% yield, respectively without the cleavage of the *N*-protecting group.

Scheme 3. Effect of the *N*-Substituent of *N*-arylpropiolamides in Acid-Triggered Oxidative Cascade Addition – Spirocyclization – Dearomatization Process

Then, we investigated the reactivity of other ketones in this acid-mediated oxidative radical cascade reaction (Scheme 4). Acetone underwent cascade reaction with *N*-methyl-*N*,3-diphenylpropiolamide or *N*-ethyl-*N*,3-diphenylpropiolamide to afford the azaspiro[4.5]trienones **6** and **7** in good yields. Going from primary to secondary ketones, a decrease of reactivity is observed as the spirocyclization with diethyl ketone afforded the product **8** in only 49% yield. This lack of reactivity could be attributed to steric factors. Unsymmetrical 1-cyclopropylethan-1-one showed a preference for radical formation at the primary carbon, giving the corresponding cyclized product **9** in 68% yield. It is important to note that even under these radical conditions the cyclopropyl group remains intact at the end of the reaction. This observation, suggested that the formation of carbon-centered radical *via* the decomposition of alkenyl peroxide is faster at primary carbon than tertiary carbon. Other unsymmetrical ketones such as hexan-2-one or dodecan-2-one displayed the same trend of reactivity and selectively reacted at the primary carbon yielding the targeted compounds **10** and **11** in 76% and 63% yield, respectively. This spirocyclization cascade reaction is tolerant to ester

group as from *N*-methyl-*N*,3-diphenylpropiolamide and methyl levulinate, a bio-sourced ketone, the cyclized product **12** is isolated in 52% yield. However, no reaction occurred when (substituted) acetophenones are employed as reactants owing such ketones have more pronounced radical cation characters (see supporting information for more details).^[20]

Scheme 4. Scope of the Ketones in Acid-Triggered Oxidative Radical Cascade Addition – Spirocyclization – Dearomatization Process.

To further explore the scope of this radical cascade spirocyclization reaction, various substituted *N*-arylpropiolamides are investigated under the optimized reaction conditions with pinacolone as radical precursor (Scheme 5). Firstly, the impact of *ortho*-substituents on aniline unit of *N*-arylpropiolamide is investigated. When the cascade reaction is performed with *ortho*-C-halo (halo = F, Cl, Br) substituted substrates, the azaspiro[4.5]trienones **13–15** are obtained in moderate to good yields without cleavage of the C-halo bonds allowing further transformations. From *ortho*-phenyl substituted *N*-phenylpropiolamide the cascade reaction, **16** is obtained in 77% yield. The reaction is slightly sensitive to the steric effect. Indeed, from *N*-arylpropiolamides, in which the aniline moiety bears two electron-donating groups (e. g., Et or *i*Pr) at both *ortho*-positions, the corresponding cyclized products **17** and **18** are obtained in 42% and 54% yield, respectively. Bromo or even iodo atom at the *meta*-position of the aniline unit are also tolerated affording the desired products **19** and **20** in good yields. Notably, when the reaction is performed using a substrate with a methyl group attached to the triple bond, *N*-methyl-*N*-phenylbut-2-ynamide, the acid-

mediated radical cascade spirocyclization with pinacolone failed to deliver the corresponding azaspiro[4.5]trienone **21**. However, substituent on the aryl group attached to the triple bond are well-tolerated. As example *p*-hexyloxy substituted aryl alkyne delivered **22** in 62% yield, and *o*-phenyl-substituted aryl alkynes gave the corresponding product **23** in 57% yield. Naphthalen-1-yl alkyne was also viable to furnish **24**.

Scheme 5. Scope of the *N*-arylpropiolamides in Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process

Interestingly, the reaction with *N*-arylpropiolamides containing an aniline unit substituted by a *para*-methoxy or a *para*-fluoro group afforded **1** in moderate yields (Scheme 6). Moreover, the reaction with substrates bearing a *para*-chloro or *para*-bromo substituent to the amide moiety also give **1**, albeit in a poor yield (16-24%). Whereas, no reaction occurred with substrates bearing a *para*-methyl substituent. We attributed these results to the addition of the *tert*-butylperoxy radical to the *para*-position of the phenyl group, forming a C–O bond and leading to cleavage of the C–OMe, or C–X (X = F, Cl, Br) bonds to yield

MeOH, and HX, respectively, prior to final elimination of *t*BuOH to afford the desired products (Scheme 8).

Scheme 6. Reactivity of *N*-Arylpropiolamides Bearing a *para*-Substituent on the Aniline Unit in Acid-Triggered Oxidative Radical Cascade Addition – Spirocyclization – Dearomatization Process.

Several control experiments are carefully carried out to gain deep insight into the reaction pathway. Firstly, azaspiro-[4.5]trienone (**1**) is not observed when 2 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, is added into the reaction system. However, the ketone-TEMPO adduct **22** is detected by GC-MS analysis. This observation confirms that the cascade spirocyclization involves ketone radical species (Scheme 7a). From (*d*₆)-acetone KIE values of 1.50-1.06 are determined from intermolecular competition reaction and from two parallel reactions.^[21] These results indicate that the formation of carbon-centered radical *via* the decomposition of alkenyl peroxide is not the rate-determining step (Scheme 7b). Finally in the presence of 1 equivalent of water-¹⁸O, the azaspiro-[4.5]trienone (**1**) is obtained in only 45% yield an no ¹⁸O-labeled product was detected by GC-MS analysis (Scheme 7c). This labeling experiment indicated that the oxidation of aniline moiety mostly occurred *via* the action of *tert*-butylperoxy radical (*t*BuOO•) rather than a water attack.^[10]

Scheme 7. Control Experiments

On the basis of this study and previous reports,^[4-11] a plausible mechanism is proposed (Scheme 8). Firstly, in the presence of a strong acid (*p*-TsOH), alkenyl peroxide intermediate **B**, is formed after addition of *t*BuOOH to the ketone and dehydration. Then, the decomposition of alkenyl peroxide **B** through homolytic bond cleavage leads to ketone radical **D** and *t*BuO[•], which latter reacts with *t*BuOOH to give *t*-BuOO[•] and *t*BuOH.^[13a] A subsequent radical addition of **C** into the alkyne at the α -position of the C=O bond of *N*-arylpropiolamide generates vinyl radical **E**, which undergoes an intramolecular radical cyclization at the *ipso*-position to give **F**. **F** is then trapped by the *tert*-butylperoxy radical (*t*BuOO[•]) to afford **G**. Finally, **H** undergoes deprotonation and the elimination of *t*BuOH to afford the desired azaspiro-[4.5]trienone derivative and *t*BuOH.

Scheme 8. Proposed Mechanism for Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process

In summary, we have developed metal-free conditions for the difunctionalization of activated alkynes with ketones. The reaction enables radical cascade addition – spirocyclization – dearomatization process initiated by the formation of ketone radicals from ketones and *tert*-butyl hydroperoxide under acidic conditions. This one-pot cascade reaction give a straightforward access to 3-(2-oxoalkyl)azaspiro-[4.5]trienones, incorporating a spirocycle unit that is a common structural motif in many natural products and pharmaceuticals.

Experimental Section

General Procedure for Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process: In an oven-dried 15 mL Schlenk tube, *N*, 3-diarylpropiolamide (0.2 mmol, 1.0 equiv.) and TBHP (1 mmol, 5.0 equiv.) (TBHP: 5.5M in the dodecane solution) were dissolved in degassed ketone (1 mL). Then, 4-methylbenzenesulfonic acid (0.02 mmol, 0.1 equiv.) was added under a stream of argon, and the reaction mixture was stirred at 60 °C over 48 h. After evaporation of solvent, the product was purified using flash column chromatography on silica gel to afford desired azaspiro[4.5]trienone products.

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