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Metal-free Spirocyclization of *N*-Arylpropiolamides with Glyoxylic Acids: Access to Complex Azaspiro-fused Tricycles

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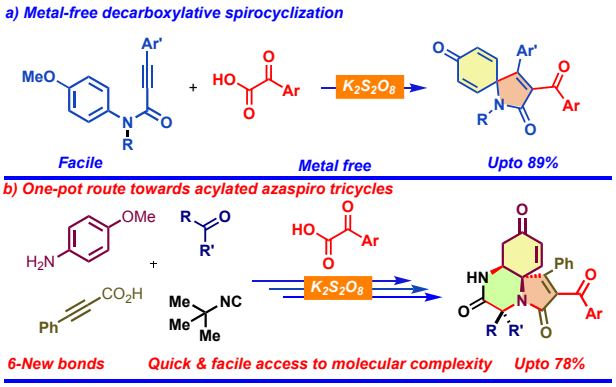
Abstract: A metal-free oxidative cascade acylation and dearomatization of *N*-(*p*-methoxyaryl)propiolamides was achieved *via* $K_2S_2O_8$ mediated decarboxylation of *α*-oxocarboxylic acids under operationally simple conditions to access azaspiro[4,5]-trienones in good to excellent yields. Furthermore, the utility of the protocol was illustrated in a one-pot reaction sequence consisting of Ugi-reaction/spirocyclization/aza-Michael transformation for the construction of complex tricyclic cores having quaternary spirocenters.

Functionalized spirocyclohexadienones have drawn much attention recently because of their excellent biological activities and their widespread applications in the synthesis of complex molecular frameworks.[1] Consequently, there is a growing demand for developing new methods for the construction of these spirocycles. Dearomatization of easily available phenol derivatives and transition-metal catalysed intramolecular nucleophilic *ipso*-carbocyclization of alkenes/alkynes were found to be versatile strategies for the generation of spirocyclohexadienone system.[2,3] Furthermore, cascade *ipso*-spirocyclization of *N*-arylpropiolamides involving either electrophilic activation[4] or radical addition[5] have emerged as fascinating synthetic protocols for constructing functionalized azaspiro[4,5]-trienones. Following these strategies, a variety of functional groups were introduced onto the azaspiro[4,5]-trienone framework.

Of late, *α*-oxocarboxylic acids (glyoxylic acids) being widely abundant and non-toxic, were extensively utilized as environmentally benign acyl surrogates.[6] Acyl radicals generated by silver catalysed decarboxylation of glyoxylic acids have been employed in a variety of elegant alkyne addition-cyclization cascades.[7] However these protocols suffer from the requirement of expensive and non-sustainable silver catalysts, thereby limiting their large scale applications. In the recent years, $K_2S_2O_8$ has emanated as a cheap, non-toxic and readily available oxidant for carrying out a plethora of C–C and C–X bond forming reaction.[8] In this regard, metal-free generation of acyl radicals *via* persulfate mediated decarboxylation of *α*-oxocarboxylic acid is gaining rapid interest.[9] Despite these elegant reports, metal free decarboxylative *ipso*-spirocyclization with glyoxylic acids to access azaspiro-[4,5]trienones remains yet elusive.[10] Recently, we demonstrated a metal free sulfonylative spirocyclization strategy towards sulfonylated azaspiro-[4,5]trienones.[5n] In continuation of this interest, herein we report an efficient metal-free, and facile route towards acylated azaspiro-[4,5]trienones *via* a persulfate mediated decarboxylative *ipso*-spirocyclization of *N*-arylpropiolamides with aryl glyoxylic acids. The strategy was further illustrated in a one-pot reaction sequence consisting of Ugi-reaction/spirocyclization/aza-Michael reaction for the synthesis of complex acylated azaspiro tricycles (Scheme 1b).



Scheme 1: Overview of the work

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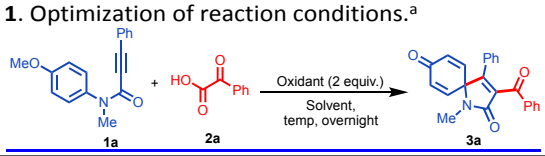
We commenced our investigation with *N*-(4-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide **1a** and phenylglyoxylic acid **2a** as the model substrates. Initially, the reaction was carried out using 20 mol% of $AgNO_3$ as a catalyst in 1:1 mixture of acetone and water at 80 °C employing $K_2S_2O_8$ as the stoichiometric oxidant and we were delighted to observe the formation of target spiro[4,5]-trienone **3a** in 28% NMR yield within 12 h (entry 1). To evaluate the roles of the silver salt and the oxidant, initial control experiments were carried out. While in the absence of $K_2S_2O_8$, as expected no reaction was observed (entry 2). Interestingly, the control experiment without $AgNO_3$ afforded **3a** in a much better yield of 43% (entry 3). Encouraged by this, various parameters like solvents, concentration and temperature were screened to improve the yield. As evident from entries 4-7, other solvents led to inferior yields. Increasing the amount of the oxidant $K_2S_2O_8$ led to slightly improved yields of 52% (3.0 equiv.) and 48% (4.0 equiv.) (entries 8-9). When the reaction was carried out at 100 °C using 3.0 equiv. of $K_2S_2O_8$, **3a** was observed in 63% yield (entry 10). Further increasing the temperature to 120 °C drastically improved the reaction efficiency and the product **3a** was formed in 91% NMR yield (89% isolated) (entry 11). Reduction of the stoichiometry of **2a** and use of other oxidants like $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ or oxone instead of $K_2S_2O_8$ led to inferior yields (entries 12-15)**.**

Table 1. Optimization of reaction conditions.[a]

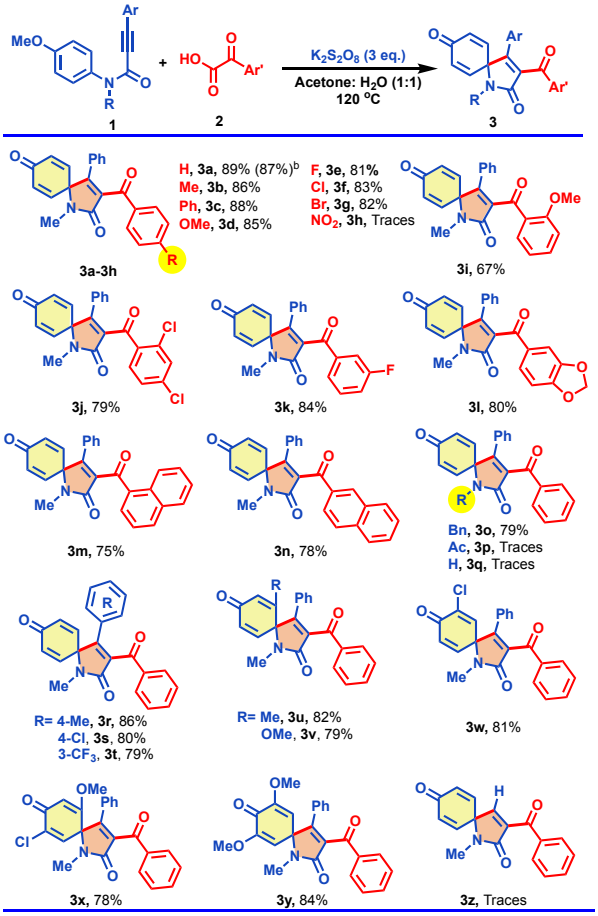


Sr.no	Cat.	Oxidant	Solvent	Temp (°C)	Yield (%)[b]
1	$AgNO_3$	$K_2S_2O_8$	Acetone:H_2O (1:1)	80	28
2	$AgNO_3$	-	Acetone:H_2O (1:1)	80	ND
3	-	$K_2S_2O_8$	Acetone:H_2O (1:1)	80	43
4	-	$K_2S_2O_8$	DMF:H_2O (1:1)	80	16
5	-	$K_2S_2O_8$	DCM:H_2O (1:1)	80	Traces
6	-	$K_2S_2O_8$	MeCN:H_2O (1:1)	80	38
7	-	$K_2S_2O_8$	THF:H_2O (1:1)	80	7
8	-	$K_2S_2O_8$	Acetone:H_2O (1:1)	80	52[c]
9	-	$K_2S_2O_8$	Acetone:H_2O (1:1)	80	48[d]
10	-	$K_2S_2O_8$	Acetone:H_2O (1:1)	100	63[c]
11	**-**	**$K_2S_2O_8$**	**Acetone:H_2O (1:1)**	**120**	**91 (89)[c,e]**
12	-	$K_2S_2O_8$	Acetone:H_2O (1:1)	120	70[f]
13	-	$(NH_4)_2S_2O_8$	Acetone:H_2O (1:1)	120	68[c]
14	-	$Na_2S_2O_8$	Acetone:H_2O (1:1)	120	74[c]
15	-	Oxone	Acetone:H_2O (1:1)	120	32[c]

Reaction conditions: a) unless mentioned, **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv.), $AgNO_3$ (20 mol%), $K_2S_2O_8$ (2 equiv.). b) Yield based on ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. c) 3.0 equiv. of $K_2S_2O_8$. d) 4.0 equiv. of $K_2S_2O_8$. e) Yield in parenthesis refers to isolated yield after column chromatography. f) 1.5 equiv. of **2a**.

Having the optimized reaction conditions in hand, the scope and limitation of this strategy were studied with **1a** against a variety of arylglyoxylic acids (Table 2). Arylglyoxylic acids bearing either electron-donating or electron-withdrawing groups in the *ortho*, *meta* or *para*-positions of the aryl ring were well tolerated, generating the corresponding products **3b-3k** in good yields (67-88%). Strong electron-withdrawing NO_2 group failed to give the desired product **3h**. Captivatingly, benzodioxolone, 1-napthyl as well as 2-napthyl glyoxylic acids reacted smoothly with **1a** delivering the respective spirocyclic trienones **3l**, **3m** and **3n** in good yields (80, 75 and 78%).

Table 2. Scope of the decarboxylative *ipso*-spirocyclization.[a]

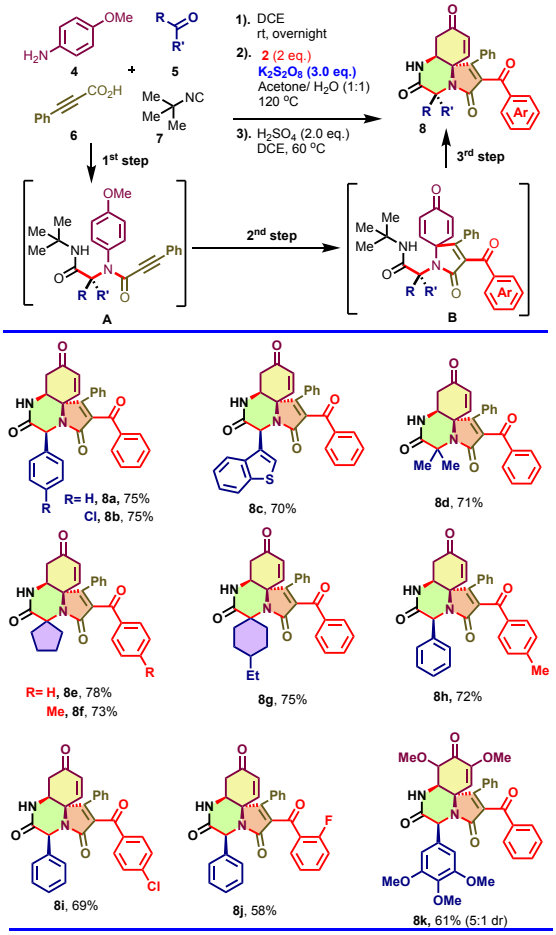


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2 equiv.), $K_2S_2O_8$ (3 equiv.), 120 °C, 12 h. [b]Isolated yield from 1.0 g (3.8 mmol) of **1a.**

Subsequently, we turned our attention to explore the scope of various *N*-(*p*-methoxyaryl)propiolamides **1** against phenylglyoxylic acid **2a**. Initially the effect of protecting group on the nitrogen atom of **1** was investigated. While *N*-benzyl protection on nitrogen atom delivered the desired product **3o** in 79%, reaction of **2a** with substrate having the *N*-acyl or free N-H groups met with no success (**3p** and **3q**). We then explored the effect of substituent on the aromatic ring of the internal alkyne and were pleased to find that methyl, chloro and trifluoromethyl substituted arylalkynes provided the desired products **3r**-**3t** in good yields. Substrates bearing *o*-methyl, *o*-methoxy, or *m*-chloro on the aromatic ring of *N*-aryl moiety also reacted smoothly with **2a** and afforded the corresponding products in good yields **3u-w** (79-82 %). Moreover, trisubstituted *N*-arylalkynamides (one methoxy and one chloro or two methoxy groups) were also found to be consistent with the optimal conditions **3x** & **3y**. The terminal alkyne bearing *N*-arylpropiolamide failed to

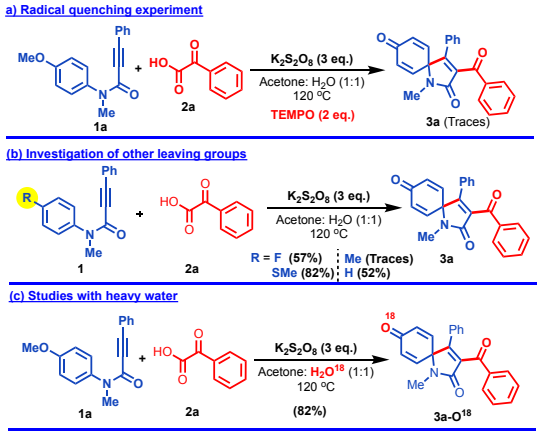
deliver the corresponding product **3z**. To our delight the reaction was found to be scalable where in 1 g of **1a** yielded 1.12 g of **3a** in 87%.

Table 3: One pot synthesis of acylated tricyclic azaspirotrienones.



Reaction conditions: 1) **4** (0.1 mmol), **5** (0.1 mmol), **6** (0.1 mmol), **7** (0.1 mmol), DCE, rt. 12 h. 2) **2** (0.2 mmol), $K_2S_2O_8$ (0.3 mmol), Acetone:H_2O (1:1), 120 °C, 12 h. 3) H_2SO_4 (0.2 mmol), DCE, 60 °C, 6 h.

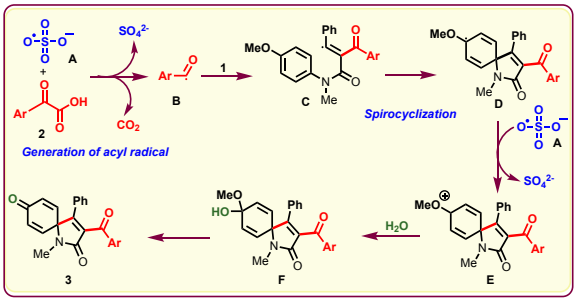
Azaspiro-fused tricyclic motifs form the core of a variety of medicinally active naturally occurring alkaloids like, cylindricines C, lepadiformine, and fasicularin.[11] To broaden the utility of the developed protocol, we envisaged to gain facile access to novel acylated azaspiro-fused tricyclic skeletons in a one-pot manner employing the decarboxylative spirocyclization. We envisioned that a four-component Ugi reaction of *p*-methoxy aniline **4**, carbonyl compounds **5**, phenylpropiolic acid **6** and *tert*-butyl isonitrile **7** would furnish the propiolamide **A**, which would be similar to propiolamide **1** and poised to undergo metal free decarboxylative *ipso*-cyclization providing the key intermediate **B,** which on acid mediated aza-Michael addition would furnish novel acylated tricycles **8** having quaternary spirocenters. To realize the same aniline **4** was reacted with benzaldehyde **5a**, propiolic acid **6** and *t*-Bu isonitrile **7** in DCE over night after which the solvent was evaporated and the crude mixture was then subjected to our optimized conditions with the glyoxylic acid **2a**. Following this the solvents were removed again and the crude mixture was treated with acid in DCE and heated to 60 °C. We were delighted to observe the formation of the desired acylated tricycle **8a** in 75% as a single diastereomer, significantly increasing the value of the protocol. Indeed, high diastereoselectivities were also observed in related acid-catalyzed cyclization reported by Srivastava and co-workers and the stereochemical assignment of azaspiro tricycles **8** was done in analogy with the results of Srivastava and co-workers.[12] Remarkably, the overall sequence consists of formation of six new bonds and three stereocenters. Various benzaldehydes **5** were compatible with the one-pot sequence **8b** & **8c**. To our delight, we found that aldehydes could be replaced with ketones, wherein acetone was also found to be viable furnishing **8d** in 71%. Pleasingly, cyclopentanone and 4-ethyl cyclohexanone delivered the corresponding tetracyclic bis-spiro derivatives **8e-g** in good yields. Substituted glyoxylic acids **2** furnished the corresponding products in moderate to good yields **8h-8j.** Pleasingly, 3,4,5-trimethoxyaniline **4** and 3,4,5-trimethoxy benzaldehyde **5** were found to be compatible in the sequence affording the complex well functionalized derivatives **8k** in 61% (5:1 dr).



Scheme 2. Preliminary mechanistic studies.

In order to gain some insights on the mechanism of the reaction, preliminary studies were carried out. Addition of a radical scavenger like 2,2,6,6-tetrametyl-1-piperidinyloxy (TEMPO) in 2.0 equiv. was found to inhibit the reaction indicating that the cascade acylation might proceed *via* a radical pathway. Interestingly, under the optimized conditions, *p*-fluoro substituted *N*-phenylpropiolamide gave the desired 3-acyl azaspiro[4,5]-trienone **3a** in 57% yield while methylmercapto substitution led to the formation of **3a** in 82%. Furthermore, unsubstituted *N*-phenylpropiolamide also furnished **3a**, albeit in lower yield (52%). No product formation was observed with the *p*-methyl derivative. Since *p*-methoxy, *p*-fluoro, *p*-methylmercapto and unsubstituted *N*-phenylpropiolamides were able to deliver the spirotrienone **3a**, we sought to explore the source of oxygen atom of the newly formed carbonyl group by O^{18}-labelling experiment. Using a mixture of acetone and H_2O^{18} (1:1) as a solvent, spirotrienone **3a-O^{18}** containing predominantly O^{18} was obtained in 82% NMR yield. These findings suggest that new carbonyl oxygen originates from water.

A plausible mechanism for the metal-free acylation *ipso*-cyclization was proposed based on the previous reports and control experiments (Scheme 3).[9] Homolytic cleavage of persulfate under thermal condition produces the reactive sulfate radical anion intermediate **A.** Single electron oxidation of glyoxylic acid **2** by **A** generates acyl radical **B** after extrusion of carbon dioxide. The acyl radical **B** reacts with the propiolamide **1** generating the radical intermediate **C,** which on *ipso*-spirocyclization would form intermediate **D.** The radical intermediate **D** is oxidized by a second sulfate radical anion to generate intermediate **E**. Nucleophilic attack of water and subsequent hydrolysis of the hemiketal furnishes the acylated azaspiro-[4,5]trienone **3** *via* the intermediate **F.**



Scheme 3. Proposed mechanism.

Conclusions

In summary, a simple and versatile strategy for furnishing a wide variety of acylated azaspiro[4,5]-trienones from *N*-arylpropiolamides and α-oxocarboxylic acids has been developed under operationally simple conditions. This methodology offers a concise approach to this class of molecules under metal-free conditions and requires inexpensive and readily available $K_2S_2O_8$ as oxidant. Additionally complex tricyclic spirocycles were synthesized efficiently in a single pot by extension of the protocol. Preliminary mechanistic studies indicated that the cascade cyclization proceeds *via* a radical pathway and the oxygen atom of the newly formed carbonyl group originates from water.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Metal-free Spirocyclization of *N*-Arylpropiolamides with Glyoxylic Acids: Access to Complex Azaspiro-fused Tricycles

A. M. Nair, A. H. Shinde, S. Kumar, C. M. R. Volla*

An efficient $K_2S_2O_8$-mediated oxidative cascade spirocyclization of *N*-arylpropiolamides with aryl glyoxylic acids was demonstrated for constructing azaspiro[4,5]-trienones and complex azaspiro-fused architectures.