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Silver-catalyzed cascade cyclization and functionalization of *N*-aryl-4-pentenamides: an efficient route to γ-lactam-substituted quinone derivatives†

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The synthesis of γ-lactam-substituted quinone derivatives through a Ag_2O-catalyzed cascade cyclization and functionalization of *N*-aryl-4-pentenamides has been developed. Related 2-oxazolidinone substituted quinone products can be also obtained with *N*-aryl allyl carbamates. The reactions proceed through an amidyl radical-initiated 5-*exo*-trig cyclization and followed radical addition to quinones. They provide an efficient route to various γ-lactam-substituted quinone derivatives with a wide range of substrate scope.

Introduction

Quinone-based organic molecules are present in various natural products and have been widely used as building blocks in total synthesis because of their broad spectrum of biological activities, including antibacterial, antitumor, antimalarial and anti-inflammatory.[1] Notably, alkyl 1,4-naphthoquinones such as menadione (vitamin K_3), plumbagin, plasmodione and phytomenadione (vitamin K_1) have attracted a great deal of attention due to their relevant biological activity (Fig. 1).[2] Consequently, the development of general and efficient methodologies to incorporate functional groups into 1,4-naphthoquinones is of great importance.[3] However, common strategies that would allow access to such compounds suffer from several drawbacks. The prevailing transition-metal-catalyzed method usually works sluggishly due to the ability of quinone substrates to act as ligands and oxidants,[4] even workable examples of these underwent a Kochi–Anderson type reaction,[5] despite a few exceptions.[6] Alternative methods involving the prefunctionalization of substrates followed by deprotection have been proved time-consuming and labor-intensive.[7] Therefore, developing more general and environmentally benign methods for the functionalization of 1,4-naphthoquinone derivatives is in great demand.[8]

Amidyl radicals recently have attracted tremendous attentions as a class of highly reactive intermediates in organic synthesis.[9] In recent years, cascade cyclization and functionalization of enamides through amidyl radicals emerged as an efficient method for construction of lactam-containing molecules. Great contributions have been made by Nicolaou, Studer, Knowles, Xu, Li and others to generate amidyl radicals from *N*-aryl-4-pentenamides under various conditions.[10–15] The generated amidyl radicals immediately initiate 5-*exo*-trig cyclization to form the C-centered radical, which can be applied to diverse functionalizations (Scheme 1a). Inspired by these achievements, we envisaged that the generated radicals would be trapped by electron-deficient double bond of 1,4-naphthoquinone to directly form valuable lactam-substituted quinone derivatives. Recently we disclosure a silver-mediated tandem trifluoromethylthiolation and cyclization of *N*-aryl-3-butenamides.[16] As the extension of our current research on difunctionalization of alkenes, herein we report a silver-

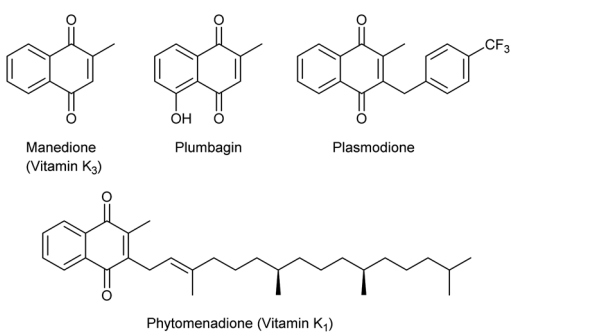

Fig. 1 Examples of 1,4-naphthoquinone derivatives with biological functions.

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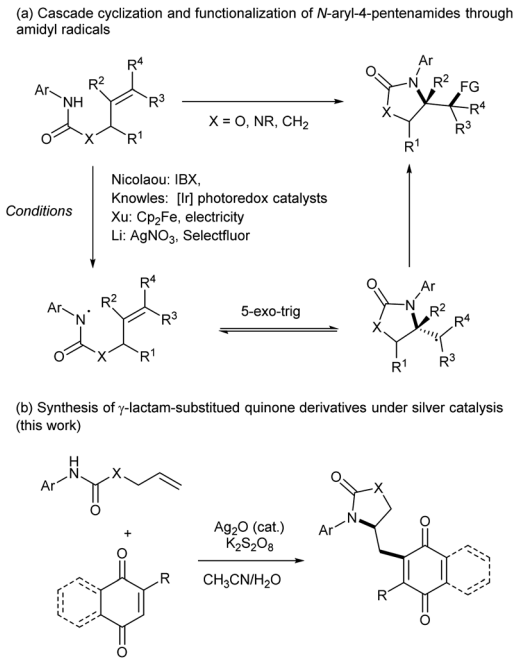


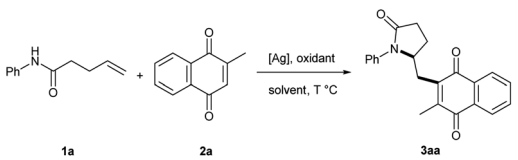
Scheme 1 Cascade cyclization and functionalization of *N*-aryl-4-pentenamides through amidyl radicals.

catalyzed cascade cyclization and functionalization of *N*-aryl-4-pentenamides with quinone, which provide an efficient route to γ-lactam-substituted quinone derivatives (Scheme 1b). Even though quinone and γ-lactam are both common and important organic motifs, to the best of our knowledge, the combination of two structures in a single molecule has never been reported.

Results and discussion

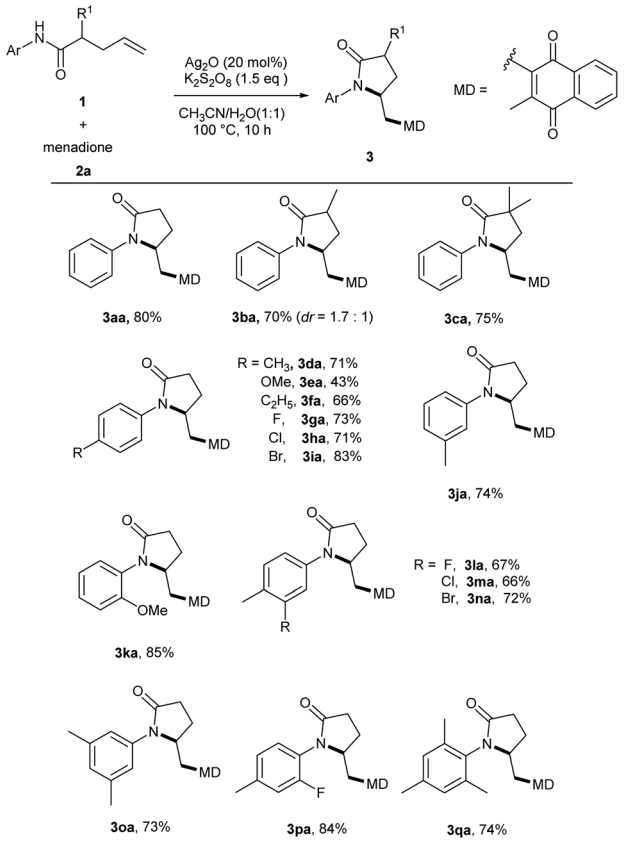
Initially, we started to explore the reaction conditions with *N*-phenyl-4-pentenamide (**1a**) and menadione (**2a**) as the model substrates (Table 1). To our delight, the desired product (**3aa**) was isolated in 33% yield in the presence of 20 mol% Ag_2O with 1.5 equiv. $K_2S_2O_8$ in DCM at 100 °C for 10 hours (entry 1). Then we set out to increase reaction yield by screening solvents. As shown in entries 2–5, although the reaction proceeded in DCE, DMSO and CH_3CN, the highest isolated yield was afforded by CH_3CN. We subsequently examined the mixed solvents (entries 6–8). The isolated yield was greatly improved from 54% to 80% in a mixture of CH_3CN/H_2O (1 : 1). Other silver salts were used, including $AgNO_3$, AgOAc, AgOTf, AgF and AgO. All of these silver salts were effective to this reaction and generated similar results (entries 9–13). Given the cost and availability, Ag_2O was chosen as the catalyst. Then a series of oxidants was examined. Other

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (20 mol%)	Oxidant (1.5 equiv)	Solvent	Yield[b] (%)
1	Ag_2O	$K_2S_2O_8$	DCM	33
2	Ag_2O	$K_2S_2O_8$	DCE	12
3	Ag_2O	$K_2S_2O_8$	DMSO	34
4	Ag_2O	$K_2S_2O_8$	THF	Trace
5	Ag_2O	$K_2S_2O_8$	CH_3CN	54
6	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (1 : 3)	70
7	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (3 : 1)	62
8	**Ag_2O**	**$K_2S_2O_8$**	**CH_3CN/H_2O (1 : 1)**	**80**
9	$AgNO_3$	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	77
10	AgOAc	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	75
11	AgOTf	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	75
12	AgF	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	72
13	AgO	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	77
14	Ag_2O	$Na_2S_2O_8$	CH_3CN/H_2O (1 : 1)	74
15	Ag_2O	$(NH_4)_2S_2O_8$	CH_3CN/H_2O (1 : 1)	76
16	Ag_2O	Oxone	CH_3CN/H_2O (1 : 1)	5
17	Ag_2O	TBHP	CH_3CN/H_2O (1 : 1)	0
18	Ag_2O	*m*-CPBA	CH_3CN/H_2O (1 : 1)	0
19[c]	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	72
20[d]	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	65
21[e]	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	70
22[f]	Ag_2O	$K_2S_2O_8$	CH_3CN/H_2O (1 : 1)	72

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol, 3 equiv.), Ag catalyst (20 mol%), oxidant (0.3 mmol, 1.5 equiv.) in solvent (2.0 mL) for 10 hours. [b] Isolated yield. [c] 120 °C. [d] 80 °C. [e] 2 equiv. of **2a**. [f] 10 mol% Ag_2O.



Scheme 2 Substrate scope of *N*-aryl-4-pentenamides (**1**).[a,b] [a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), Ag_2O (20 mol%), $K_2S_2O_8$ (1.5 equiv.) in CH_3CN/H_2O (1 : 1, 2.0 mL) for 10 h. [b]Isolated yields.

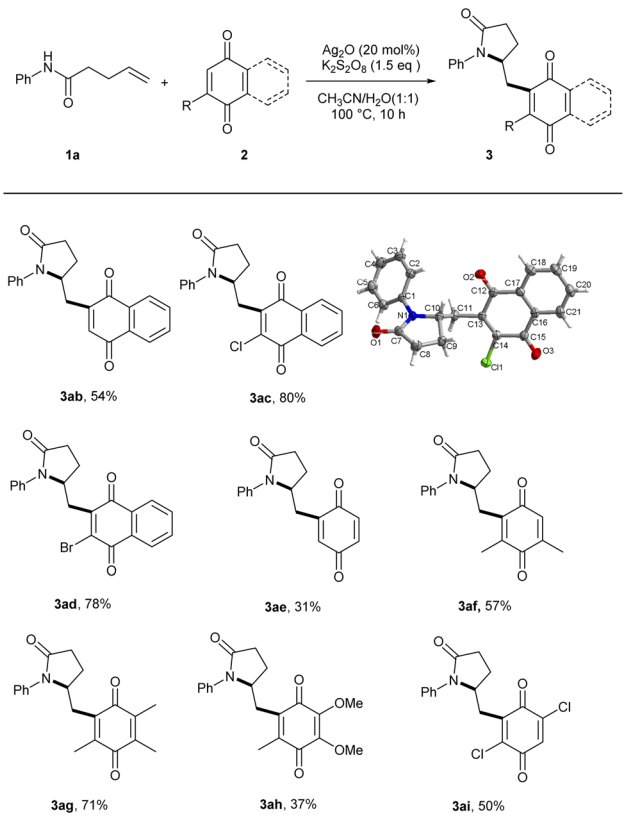
persulfate salts such as $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ showed similar reactivity as $K_2S_2O_8$, while oxone was much less efficient (entries 14–16). Organic peroxides were ineffective in this reaction (entries 17 and 18). Reaction temperature was also screened but the product yield decreased under either higher or lower temperature (entries 19 and 20). Finally, the attempts of reducing the substrate amount or catalyst loading all resulted in decreased yields (entries 21 and 22). Therefore, we decided to use the conditions in entry 8 as the optimized reaction conditions.

With the optimized conditions in hand, we first investigated the substrate scope of *N*-aryl-4-pentenamides (**1**) as shown in Scheme 2. When methyl groups substituted at the α position of amide, reaction still worked efficiently to generate the desired products (**3ba–3ca**). However, no significant Thorpe–Ingold effect was observed. For the substrates with different *N*-aryl moiety, the reaction proceeded smoothly to produce a wide variety of γ-lactam-substituted menadiones in good to excellent yields (**3da–3ka**). Either electron-donating or electron-withdrawing groups at the *para*, *meta* or *ortho* positions of aryl ring were tolerated without significant electronic effects. Moreover, a series of di-substituted or tri-substituted *N*-arylamides were also tolerated to afford the products in good to excellent yields, which shows the steric hindrance of the aryl group did not affect the efficiency of this transformation (**3la–3qa**). Furthermore, the reaction could be easily scaled up to gram level (for details, see the ESI†).

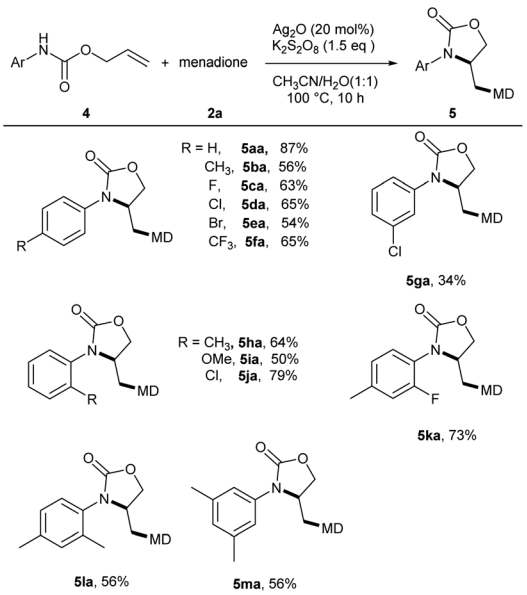
Next, the substrate scope for quinones was examined as illustrated in Scheme 3. Unsubstituted 1,4-naphthoquinone generated the mono-substituted product in moderate yield without the formation of di-substituted product (**3ab**). Higher reactivity was observed with 2-chloro- and bromo-naphthoquinones (**3ac**, **3ad**). The absolute structure of **3ac** was unambiguously determined by the X-ray diffraction analysis and other products were assigned by analogy.[17] A number of benzoquinones including alkyl, halogen, and alkoxy substituents also underwent this reaction (**3ae–3ai**). Relatively poor yields of **3ae** and **3ah** were obtained due to low conversions of their substrates.

In an effort to increase the molecular diversity, a serious of *N*-aryl allyl carbamates (**4**) was investigated as well. To our delight, these substrates were also applicable in this method and afforded the corresponding 2-oxazolidinone products (Scheme 4). The *para*-substituent effect was first evaluated. Various functionalities such as alkyl, halogen and trifluoromethyl were tolerated at *para*, *meta* or *ortho* positions of aryl ring without distinct electronic effect (**5aa–5ja**). Di-substituted *N*-arylamides could also participate in this reaction, giving the desired products in 56–73% yields (**5la–5ma**).

To gain deeper insight into the reaction mechanism, a series of experiments were conducted (Scheme 5). First, the standard



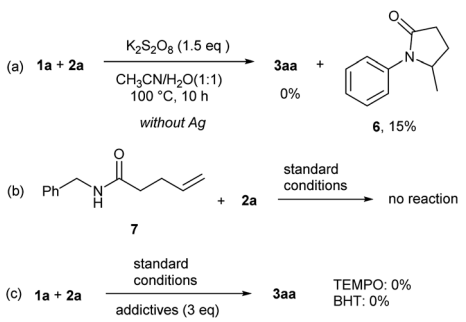
Scheme 3 Substrate scope of quinones (**2**).[a,b] [a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Ag_2O (20 mol%), $K_2S_2O_8$ (1.5 equiv.) in CH_3CN/H_2O (1 : 1, 2.0 mL) for 10 h. [b]Isolated yields.



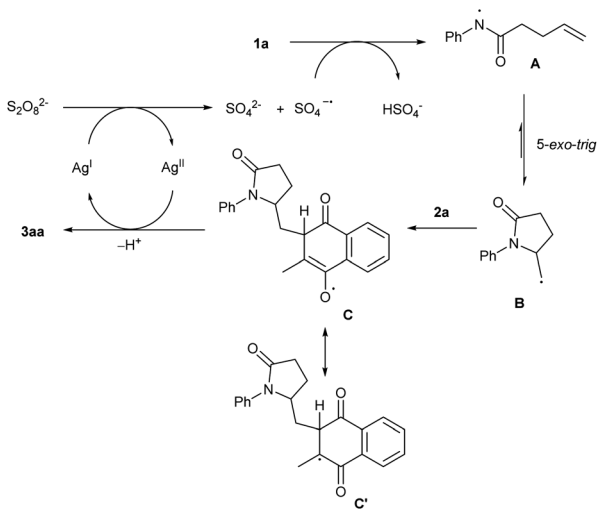
Scheme 4 Substrate scope of *N*-aryl allyl carbamates (**4**).[a,b] [a]Reaction conditions: **4** (0.2 mmol), **2a** (0.6 mmol), Ag_2O (20 mol%), $K_2S_2O_8$ (1.5 equiv.) in CH_3CN/H_2O (1 : 1, 2.0 mL) for 10 h. [b]Isolated yields.

reaction in the absence of silver was conducted. Instead of the difunctionalization product **3aa**, only a cyclization product **6** was formed with very low conversion. It indicated the critical role of silver in this transformation. Next, the reaction of *N*-benzyl-4-pentenamide (**7**) under standard conditions was examined. It failed to generate desired product, which further proved the reaction underwent a radical mechanism since aryl group is essential to the initial amidyl radical formation.[10b] Finally, radical inhibition reactions were carried out with the addition of radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT). The results showed that both regents completely inhibited the transformation, although no TEMPO or BHT intermediates were detected.

Therefore, based on the experimental results and reported literature, a plausible mechanism was proposed in Scheme 6. Initially, $SO_4^{\bullet -}$ radical was generated from persulfate with the assistance of Ag(I).[14,18] It allows hydrogen atom abstraction (HAT) of the substrate **1a** to form an amidyl radical **A**. Radical **A** readily initiates subsequent intramolecular 5-*exo*-trig



Scheme 5 Control experiments.



Scheme 6 Proposed mechanism.

cyclization to afford a carbon-centered radical **B**. The resulting radical **B** then undergoes a silver-promoted conjugated addition to the menadione to form the intermediate **C**. Finally, intermediate **C** undergoes HAT to regenerate Ag(I) and the desired products **3aa**. The role of Ag(I) in this reaction is probably to promote the generation of $SO_4^{\bullet -}$ radical and co-ordinate with the intermediate O-radical.[19]

Conclusions

In summary, we have developed a cascade cyclization and functionalization of *N*-aryl-4-pentenamides with quinones. This method allows efficient access to various γ-lactam-substituted quinone derivatives with a wide range of functional group tolerance. Relative 2-oxazolidinone substituted quinone products can be also obtained with *N*-aryl allyl carbamates. Preliminary mechanistic studies suggested that an amidyl radical is involved in this reaction. We demonstrated the utility of the amidyl radicals for the direct construction of γ-lactam and consequent installation of quinone groups, which might be potentially used to construct more complex compounds. Relevant researches are ongoing in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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