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Acid-catalyzed cascade radical addition/cyclization of arylacrylamides with ketones

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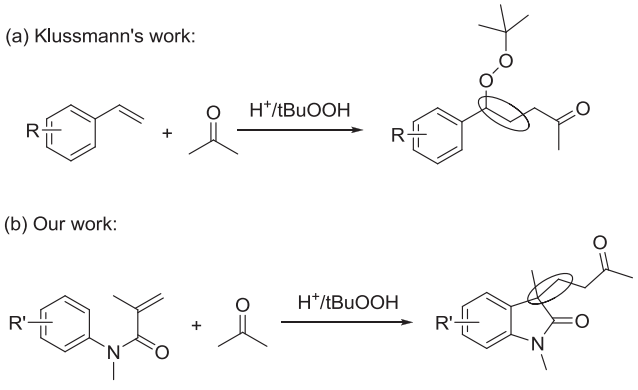
ABSTRACT

A Brønsted acid catalyzed cascade radical addition/cyclization of arylacrylamides with ketones was described. The reaction tolerates a series of functional groups, such as nitro, methoxyl, carbonyl, bromo, chloro, fluoro, and trifluoromethyl groups. γ-Peroxyketones were also prepared using *N*-arylsulfonylacrylamides as substrates under acid-catalyzed conditions.

1. Introduction

In recent years, a series of metal-catalyzed oxidative 1,2-difunctionalization of alkenes has attracted considerable attention, providing the most efficient strategy for the construction of functionalized organic compounds. [1] Owing to important bioactivity in a wide variety of natural products, pharmaceuticals, and bioactive molecules, the search for sustainable and convenient methods for the synthesis of oxindoles is of constant interest in modern organic synthesis. [2] Very recently, many cascade methods employing oxidative cross-couplings to bifunctionalized alkene substrates, followed by cyclization to produce oxindoles derivatives have been achieved. [1f]Among which, the radical alkylarylation, [3]arylcarbonylation, [4]azidoarylation, [5]nitroarylation, [6]arylphosphorylation, [7]arylsulfonylation, [8]and aryltrifluoromethylation[9] of *N*-arylacrylamides have since been reported by several groups, allowing the direct formation of oxindole frameworks. To the best of our knowledge, these protocols using ketones as alkyl radicals were not well-documented. For instance, in 2013, Duan group reported an efficient silver-catalyzed oxidative cyclization of acrylamides with carbonyl compounds. [3e] Ji group reported a metal-free oxidative radical addition of carbonyl compounds to α,α-diaryl allylic alcohols. [10]In 2014, Klussmann group discovered that under a Brønsted acid catalyzed conditions, ketone radicals could be utilized to develop a multicomponent radical addition of *tert*-butyl hydroperoxide (TBHP) to olefins (Scheme 1-a). [11]Herein, we envisioned that this metal-free catalytic conditions can realize cascade radical addition/cyclization of arylacrylamides with ketones to obtain oxindoles derivatives (Scheme 1-b).



Scheme 1. Acid-catalyzed radical addition.

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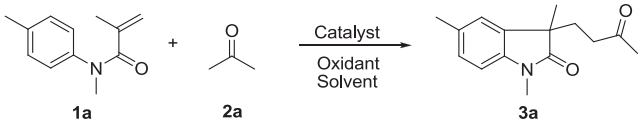
2. Results/discussion

To test the feasibility of our hypothesis, we examined the reaction of *N*-arylacrylamide **1a** with acetone **2a** under various conditions, and the results are summarized in Table 1. Using 10% TsOH as catalyst, 3 equiv TBHP (5–6 M in decane) as oxidant, acetone as solvent, a 40% target product **3a** was obtained (Table 1, entry 1). Encouraged by the initial results, the screening of oxidants, catalysts, as well as catalyst loadings has been investigated to establish the optimized reaction conditions. When the loading of TBHP was increased to 4 equiv, a 61% product **3a** was separated (entry 2). The reaction failed using 1 atm oxygen as oxidant. Using 4 equiv H_2O_2 as oxidant, the product **3a** can be produced in 22% yield. When 4 equiv TBHP (70% w in water) was used, a 65% product **3a** was obtained. Other acids such as $MeSO_3H$, CF_3COOH, and HCl were also tried, and 10% $MeSO_3H$ gave a better result (entry 6). When 10 equiv acetone was used in CH_3CN as cosolvent, a lower yield was obtained (entry 7). Last, in the absence of acid, no product was detected. It is worth mentioning that when 5 mmol of **1a** was used, a 58% yield of **3a** was obtained, indicating that this method is scalable (entry 11).

Table 1
Optimization of reaction conditions for **3a**[a]

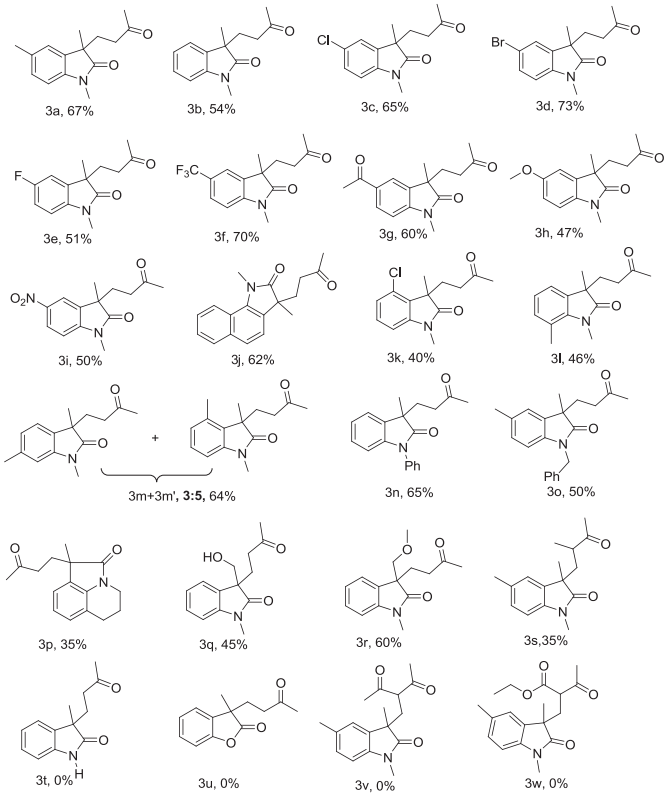


1a **2a** **3a**

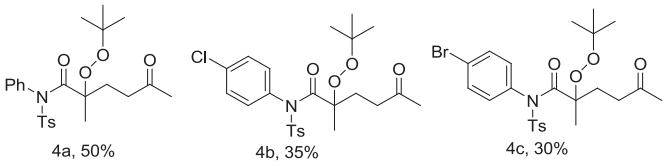
Entry	Catalyst	Oxidant	Solvent	T [°C]	Yield (%)[b]
1	10% TsOH	3 equiv TBHP	Acetone	60	40%
2	10% TsOH	4 equiv TBHP	Acetone	60	61%
3	10% TsOH	1 atm O_2	Acetone	60	0
4	10% TsOH	4 equiv H_2O_2	Acetone	60	22%
5	***10% TsOH***	***4 equiv TBHP (70% w in water)***	***Acetone***	***60***	***65%***
6	***10% $MeSO_3H$***	***4 equiv TBHP***	***Acetone***	***60***	***67%***
7[c]	10% $MeSO_3H$	4 equiv TBHP	CH_3CN	80	30%
8	10% CF_3COOH	4 equiv TBHP	Acetone	60	15%
9	10% HCl	4 equiv TBHP	Acetone	60	20%
10	—	4 equiv TBHP	Acetone	60	0%
11[d]	10% TsOH	4 equiv TBHP (70% w in water)	Acetone	60	58%

Bold and italic indicates the best reaction conditions of the reaction.
[a] Reaction conditions: **1a** (0.3 mmol), TBHP (5–6 M in decane), and solvent (2.0 mL), 12 h.
[b] Isolated yield.
[c] 10 equiv acetone was used.
[d] 5 mmol **1a** was used in 5 mL acetone, 24 h.

With the optimized conditions in hand (Table 1, entry 6), we next set out to explore the substrate scope and the limitations of the alkylcarbocyclization reaction (Scheme 2). The effect of various substitution patterns on the *N*-aryl moiety was firstly investigated including fluoro, chloro, bromo, nitro, methoxyl, acetyl, trifluoromethyl and methyl substituents, and the corresponding products were obtained in moderate to good yields. The naphthyl group was also tolerated in this reaction, and a 62% product **3j** was produced. When the substituent Cl was substituted in the *meta* position, a mixture of isomers was observed, and only the major isomer **3k** can be separated. Similarly, a mixture of **3m** and **3m′** (3:5) isomers were obtained when the methyl group was substituted in the *meta* position. *N*-arylacrylamide **1l** bearing an *ortho*-substituted methyl group was also tried, and the desired oxindole **3l** was obtained in moderate yield. It was found that N-protected substrates, such as phenyl and benzyl, could be used as effective substituent groups for this transformation (**3n** and **3o**). Tetrahydroquinoline derivative under the oxidative conditions successfully yielded the desired tricyclic oxindole **3p** in 35% yield. Notably, the CH_2OH substituent was well tolerated in this reaction. 2-(methoxymethyl)-*N*-methyl-*N*-phenylacrylamide was also a suitable substrate, and a 60% product **3r** was obtained. An asymmetric ketone like butan-2-one showed a preference for radical formation at the secondary carbon, giving the major product **3s** in 35% yield. However, N-free *N*-arylacrylamides and phenyl methacrylate were failed in this reaction. When 1,3-dicarbonyl compounds were used in the reaction system, no target products were detected (**3v** and **3w**). Interestingly, when *N*-Ts-*N*-arylacrylamides were used as substrates, γ-peroxyketones were produced in moderate yields (Scheme 3).

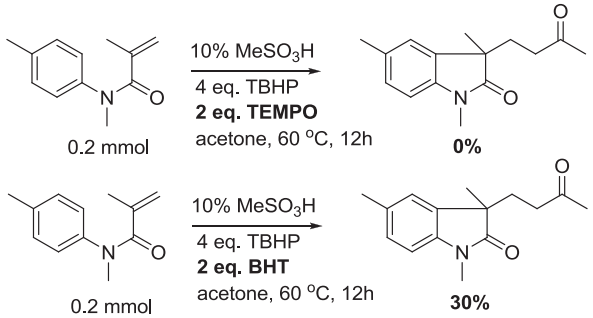


Scheme 2. Scope of acid-catalyzed cascade radical addition/cyclization.



Scheme 3. The synthesis of γ-peroxyketones.

To gain further understanding about the reaction mechanism, inhibition experiments were conducted (Scheme 4). When 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was



Scheme 4. Mechanistic experiments.