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Hydroxyalkylation-Initiated Radical Cyclization of *N*-Allylbenzamide for Direct Construction of Isoquinolinone

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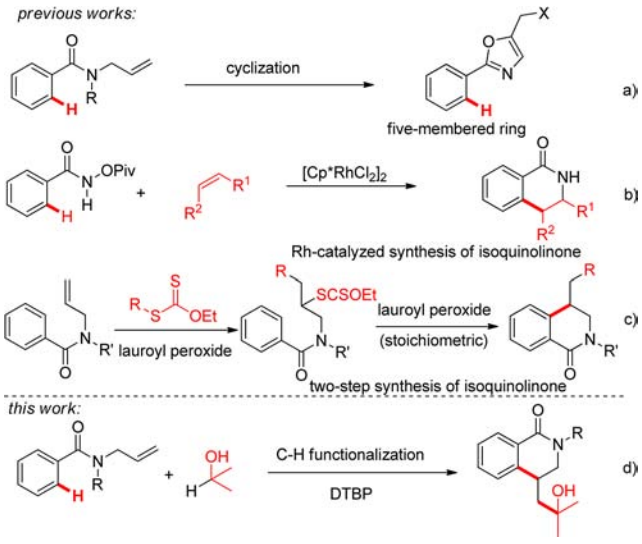
Supporting Information

ABSTRACT: A metal-free hydroxyalkylation-initiated radical six-membered heterocycle formation reaction of *N*-allylbenzamide is developed. This reaction proceeds through C(sp^3)−H bond cleavage, oxyalkylation of the double bond, and intramolecular cyclization, which provides a new route toward 4-substituted 3,4-dihydroisoquinolin-1(2*H*)-one derivatives.

N-Allylbenzamide is prevalent in organic compounds and represents an important and extremely valuable synthetic block in organic synthesis.[1,2] As a privileged building block, the allyl group allows the introduction of different functional groups into *N*-allylbenzamide via cross-coupling or addition reactions.[3] Therefore, the development of an efficient method for functionalization of *N*-allylbenzamide is of great interest and continues to attract the attention of the synthetic community. Recently, several transformations of the allyl group in *N*-allylbenzamide have been explored, such as hydroformylation,[4] reduction,[5] hydrofluorination,[6] arylation,[7] metathesis,[8] and other reactions.[9] Furthermore, cascade intramolecular cyclization of *N*-allylamide renders this organic synthetic intermediate more attractive due to the easy construction of substituted five-membered heterocycles (Scheme 1a).[10]

Scheme 1. Heterocycle Construction



In recent years, the C−H bond functionalization reaction has emerged as a viable method to construct complex molecules due to high atom-economy and readily available starting materials.[11] Direct functionalization of the C(sp^3)−H bond adjacent to an oxygen atom is extremely important in organic synthesis, as functionalized ethers widely exist in natural products and bioactive compounds.[12] Tu and other groups have developed elegant examples on cascade C(sp^3)−H bond functionalization and addition reaction of several alkenes and alkynes affording hydroalkylation products.[13] Furthermore, hydroxyalkylation triggered cascade radical cyclizations have been demonstrated to be powerful for the synthesis of five- and six-membered cyclic products of a wide range of structural varieties.[14]

Inspired by these elegant works and our interest in developing a high efficient radical cyclization method for the synthesis of heterocycles, we would like to develop a cascade C−H bond functionalization and radical cyclization reaction of *N*-allylbenzamide for the synthesis of six-membered heterocycles. To the best of our knowledge, there is no report on C−H bond functionalization initiated cyclization of *N*-allylbenzamide to assemble six-membered heterocyclic derivatives. It was noticed that the Guimond group reported an efficient rhodium(III)-catalyzed 3,4-dihydroisoquinolone synthesis from hydroxamic acids and substituted alkenes (Scheme 1b).[15] The Zard group reported an elegant work on the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one through the radical addition and cyclization reaction (Scheme 1c).[16] Also, some other useful methodologies have been developed for constructing 3,4-dihydroisoquinolin-1(2*H*)-one.[17,18] Herein, we reported a facile metal-free hydroxyalkylation initiated radical cyclization reaction between alcohols and *N*-allylbenzamide to assemble the 4-hydroxyalkyl-substituted 3,4-dihydroisoquinolin-1(2*H*)-one, which proceeded through the sequence of

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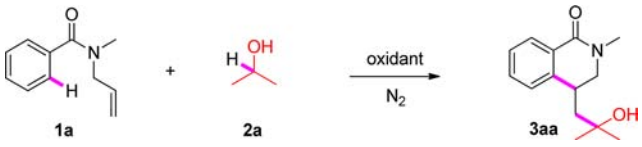
C(sp^3)−H bond cleavage, oxyalkylation of double bond, and intramolecular cyclization (Scheme 1d).

Initially, *N*-allyl-*N*-methylbenzamide (**1a**) and 2-propanol (**2a**) were selected as model substrates for the condition optimization of this radical cyclization reaction (Table 1). The

Table 1. Optimization of Reaction Conditions[a]



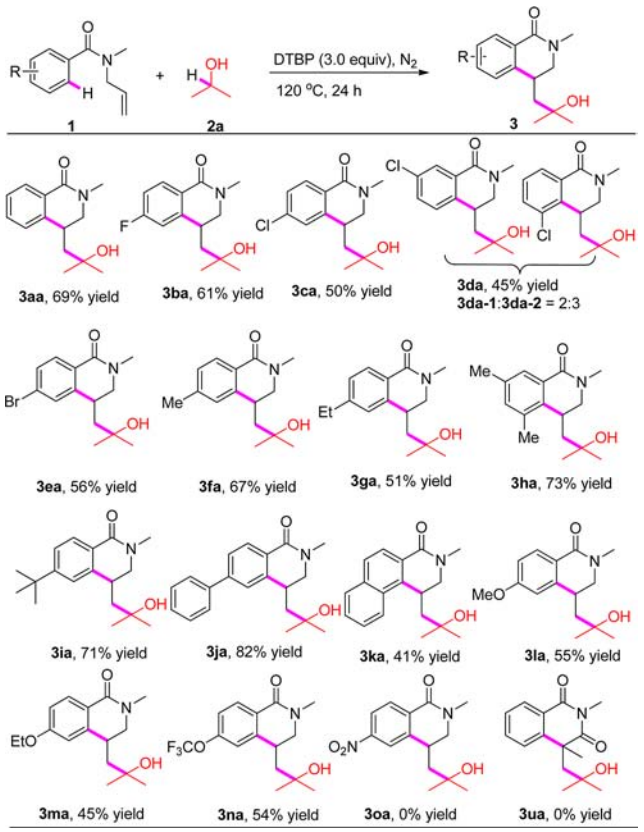
entry	oxidant (equiv)	temp (°C)	yield[b] (%)
1	TBHP (3.0)[c]	120	35
2	TBHP (3.0)[d]	120	32
3	TBPA (3.0)[e]	120	47
4	TBPB (3.0)[f]	120	44
5	DCP (3.0)[g]	120	33
6	BPO (3.0)[h]	120	ND
7	$K_2S_2O_4$ (3.0)	120	ND
8	DDQ (3.0)[i]	120	ND
9	O_2 (1 atm)	120	ND
10	DTBP (3.0)[j]	120	69
11	DTBP (1.0)	120	41
12	DTBP (2.0)	120	60
13	DTBP (5.0)	120	43
14	DTBP (3.0)	100	25
15	DTBP (3.0)	120	13[k]
16	DTBP (3.0)	120	trace[l]
17	DTBP (3.0)	120	15[m]

[a]Standard conditions: *N*-allyl-*N*-methylbenzamide **1a** (0.5 mmol), 2-propanol 2.5 mL, oxidant, 24 h, under N_2. [b]Isolated yield based on *N*-allyl-*N*-methylbenzamide. [c]TBHP = *tert*-butyl hydroperoxide, 5.0−6.0 M in decane. [d]70% solution in water. [e]TBPA = *tert*-butyl peroxyacetate. [f]TBPB = *tert*-butyl peroxybenzoate. [g]DCP = dicumyl peroxide. [h]BPO = benzoyl peroxide. [i]DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [j]DTBP = di-*tert*-butyl peroxide. [k]**1p** and 10 mol % CuI were used. [l]**1p** and 10 mol % Cu_2O were used. [m]**1p** and 10 mol % $FeBr_2$ were used.

reaction between **1a** and 2-propanol by using TBHP as the oxidant at 120 °C under nitrogen did happen, affording the expected 4-substituted 3,4-dihydroisoquinolin-1(2*H*)-one (**3aa**) in low yields (entries 1 and 2). Then, several regular oxidants were scanned for this transformation. DCP also could trigger the radical reaction, resulting in 33% chemical yield (entry 5). We were pleased to find that the reaction with TBPA and TBPB gave better results, and higher chemical yields were obtained (entries 3 and 4). Very surprisingly, we found that the reaction did not happen at all in the presence of BPO, $K_2S_2O_4$, DDQ, and oxygen (entries 6−9) and afforded almost no product. A dramatically increased yield was obtained when DTBP was used as the oxidant for this reaction (entry 10). Next, we decided to screen the loading amount of DTBP to further improve the chemical yields in the reaction. Unfortunately, changing the amount of DTBP was rather futile as the results presented in entries 10−13 clearly suggest that 3.0 equiv is the best choice. Finally, the attempt to run the reaction at lower temperature did not lead to any improvement of chemical yield (entry 14). Several metal catalysts have been used in this reaction, but no improvement was obtained (entries 15−17).

Next, we used the optimized reaction conditions to examine the structural generality of the cyclization reaction (Scheme 2).

Scheme 2. Reaction Scope of *N*-Allyl-*N*-methylbenzamide with 2a[a]



[a]Standard conditions: *N*-allyl-*N*-methylbenzamide **1** (0.5 mmol), 2-propanol 2.5 mL, DTBP 3.0 equiv, 120 °C, 24 h, under N_2. Isolated yield based on **1**.

As shown in Scheme 2, the radical cyclization reaction tolerated a wide scope of *N*-allyl-*N*-methylbenzamide derivatives and proceeded smoothly to give the expected 4-(hydroxyalkyl)-3,4-dihydroisoquinolin-1(2*H*)-one **3** in moderate to good yields. For the cases of *para*-substituted *N*-allyl-*N*-methylbenzamide derivatives, the electronic properties of the substituent have almost no apparent effect on the yields of these reactions, and several electron-donating groups (**3fa**, **3ga**, **3ia**, **3la**, **3ma**) and electron-withdrawing groups (**3ba**, **3ca**, **3ea**) were well tolerated in this reaction. To investigate the regioselectivity of this cyclization process, the reaction with the substrate *meta*-substituted group (**2d**) was conducted, resulting in a slightly lower chemical yield (45%, **3da**). The reaction showed almost no regioselectivity, and the ratio of the two isomers was 2:3. In the case of disubstituted substrate **2h**, the reaction took place smoothly, affording products **3ha** in good chemical yield (73%). It was noticed that the reaction of bulky *tert*-butyl-containing substrate **2i** also proceeded well and afforded the expected product in good chemical yields. Unfortunately, for the substrate with *p*-NO_2 substituted phenyl group **2o**, the reaction failed to give the desired product. The substrate with an electron-withdrawing substituent on the double bond (**1u**) was also used in the reaction. However, no desired product **3ua** was obtained.

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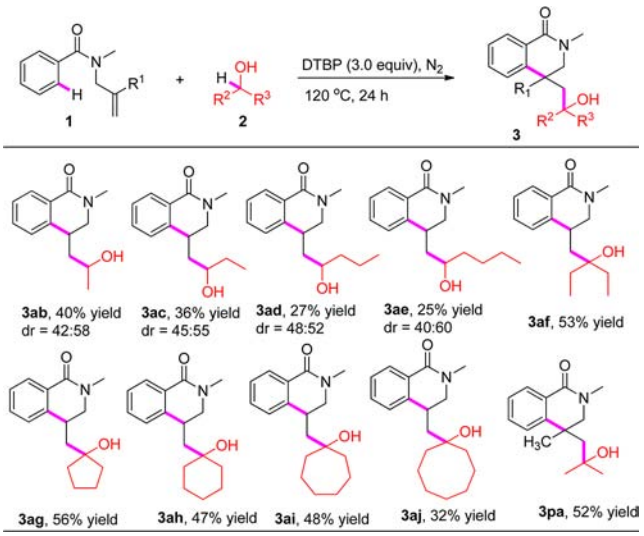
Further substrate scope study for this radical cyclization reaction was carried out by using various alcohols as substrates (Scheme 3). To this end, we selected structurally different

Scheme 3. Reaction Scope of Alcohol with 1[a]

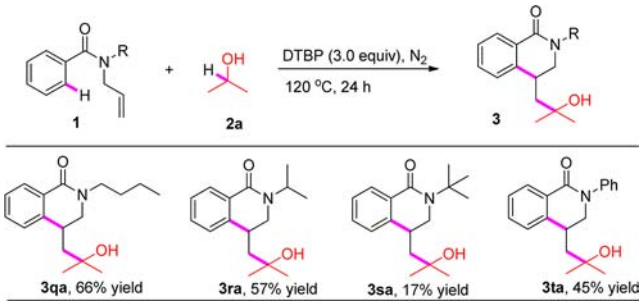


[a]Standard conditions: *N*-allyl-*N*-methylbenzamide **1** (0.5 mmol), alcohol 2.5 mL, DTBP 3.0 equiv, 120 °C, 24 h, under N_2. Isolated yield based on **1**.

starting alcohols **2** containing open-chain and cyclic moieties. It was found that the primary alcohols (**2b**–**e**) could react with *N*-allyl-*N*-methylbenzamide **1a** and initiated the intramolecular cyclization to afford the expected product. Noticeably, the yield became lower when the length of the alkyl chain increased, and only 25% yield was obtained when pentan-1-ol was used as substrate (**3ae**). Unfortunately, the reactions with these primary alcohols did not show any diastereoselectivities (**3ab**–**ae**). The secondary alcohols were also well tolerated in this reaction (**3af**–**aj**), affording slightly higher chemical yields. The similar trend also was observed for the cyclic alcohols, and the larger membered ring gave lower chemical yields. The lowest yield was found when cyclooctanol was used for this reaction (32% yield, **3aj**). Finally, substrate with substituted double bond (**1p**) was used to examine the steric effect of this reaction. It cleanly reacted with isopropanol furnishing target product **3pa**, but with a lower yield comparing to that of **3aa** (52% vs 69%). The chemical structure of product **3** has been confirmed by the single-crystal X-ray analysis of **3pa** (see the Supporting Information).

Finally, the substrate scope with the variation on nitrogen of **1** was investigated (Scheme 4). Several alkyl and aryl substituents bulkier than methyl were used to examine the effect of steric hindrance. As shown in Scheme 4, the substrate with a *N*-butyl group could react well with 2-propanol to give the corresponding product in 66% yield (**3qa**). However, a slightly lower yield was found when a bulkier isopropyl group was used as the substituent (57%, **3ra**). The very poor chemical yield in the case of **1s** bearing a *tert*-butyl substituent on the nitrogen atom can be explained by high steric hindrance, which inhibits the intermolecular radical addition (17%, **3sa**). It was noticed that a phenyl substituent also was tolerated in this reaction, and the corresponding product was obtained in a moderate yield (45%, **3ta**).

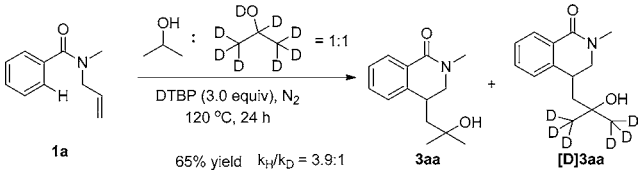
Scheme 4. Reaction Scope of 1 with Variation on Nitrogen[a]



[a]Standard conditions: *N*-allylbenzamide **1** (0.5 mmol), 2-propanol 2.5 mL, DTBP 3.0 equiv, 120 °C, 24 h, under N_2. Isolated yield based on **1**.

The final goal of this study was the mechanism investigation. The reaction was inhibited when it was carried out in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which shows that radical intermediates are involved in this transformation. In addition, the mixture of 2-propanol and [D]-2-propanol was used as radical precursor to perform the intermolecular competing kinetic isotope effect (KIE) experiment (Scheme 5). The yield was 65% with a ratio of 3.9:1 (k_H:k_D). This clearly discloses that the cleavage of the C(sp^3)–H bond may be one of the rate-determining steps in this transformation.

Scheme 5. KIE Study



We next suggested a plausible reaction mechanism to account for the above results in this cascade hydroxyalkylation-initiated radical cyclization reaction of *N*-allylbenzamide (Scheme 6). According to previous research on the functionalization of the C–H bond of alcohol,[13d,14] the 2-propanol radical intermediate **B** is formed through the reaction between intermediate **A** and **2a**. Intermediate **B** adds to the double bond of **1a** to generate the intermediate **C**, which undergoes the intramolecular cyclization to give intermediate **D**. Deprotonation of intermediate **D** results in a radical anion **E**. Finally, radical anion **E** reacts with DTBP via a single-electron-transfer process furnishing the product **3aa** and the *tert*-butoxy radical **A** for the next cycle.

In summary, a metal-free cyclization reaction proceeding through cascade C(sp^3)–H bond cleavage, oxyalkylation of the double bond, and intramolecular cyclization was developed. This hydroxyalkylation-initiated radical cyclization of *N*-allylbenzamide shows excellent functional group tolerance, which represents the first atom-economic example of construction of a six-membered heterocycle starting from *N*-allylbenzamide. This reaction provides a new route toward a class of 4-substituted 3,4-dihydroisoquinolin-1(2*H*)-one derivatives with good chemical yields.

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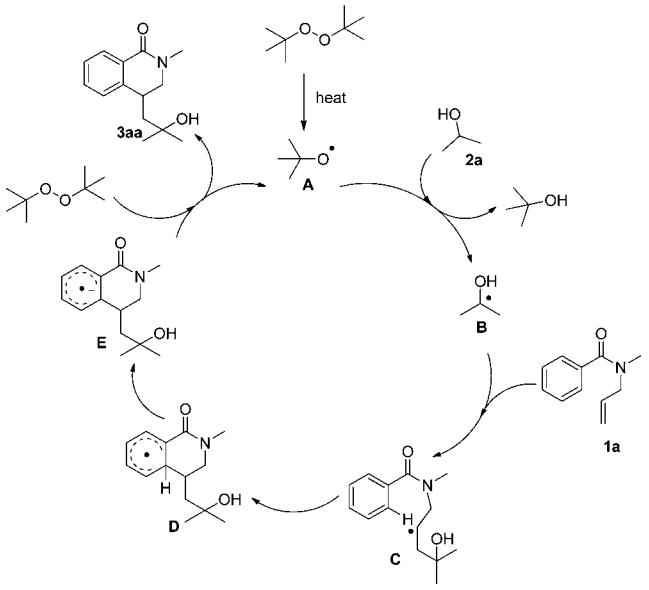
Scheme 6. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for compounds **3**, copies of ^{1}H NMR and ^{13}C NMR spectra, and single-crystal X-ray analysis data for **3pa**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01140.

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Notes

The authors declare no competing financial interest.

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