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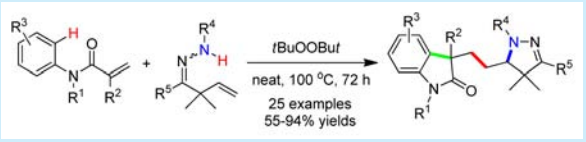
Hydrazonyl Radical-Participated Tandem Reaction: A Strategy for the Synthesis of Pyrazoline-Functionalized Oxindoles

Xiao-Yong Duan, Xiu-Long Yang, Pan-Pan Jia, Man Zhang, and Bing Han*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, P. R. China

Supporting Information

ABSTRACT: An efficient and practical tandem cyclization/addition/cyclization strategy is developed for the initial generated hydrazonyl radicals derived from the oxidation of β,γ-unsaturated hydrazones. By using this protocol, structurally novel pyrazoline-functionalized oxindoles are prepared by the reaction of easily accessible β,γ-unsaturated hydrazones with *N*-aryl acrylamides under the metal- and solvent-free conditions of DTBP (di-*tert*-butyl peroxide) via a tandem intra/intermolecular C−N/C−C/C−C bond formation.

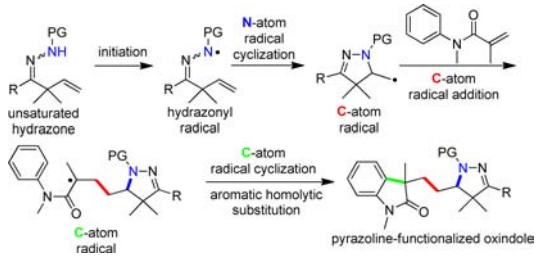


Free radical chemistry has ushered in a new epoch in the evolution of chemistry, and it has become an important and effective tool in organic synthesis in the recent decades.[1] Among the diverse free radical-mediated synthetic methodologies, strategy utilizing free radical tandem reactions has proven to be highly valuable for the synthesis of complex carbo- and heteropolycyclic skeletons because of their highly synthetic efficiency and simple operation.[2]

Hydrazonyl radical, as a kind of fascinating nitrogen-centered radical,[3] which can be easily initiated from the most common hydrazone, has not received the attention it deserves, and its considerable synthetic potential has remained largely unappreciated.[4] Very recently, we and other groups have developed a series of hydrazonyl radical-involved cyclization reactions for the synthesis of pyrazoline derivatives.[5] However, the research is far from exhaustive and much remains to be explored. In our continuous interest in the hydrazonyl radical-based reactions for a synthetic purpose, herein we wish to report an efficient and practical hydrazonyl radical-participated cascade cyclization/addition/cyclization strategy for the preparation of pyrazoline-functionalized oxindoles from easily accessible β,γ-unsaturated hydrazones and *N*-aryl acrylamides. We anticipated that the carbon-centered radical derived from the β,γ-unsaturated hydrazonyl radical 5-*exo*-*trig* cyclization would undergo intermolecular addition to the carbon−carbon double bond of *N*-aryl acrylamide to produce a deuterogenic carbon-centered radical adduct; the latter further cyclized to the adjacent *N*-phenyl via intramolecular aromatic homolytic substitution[6] to yield pyrazoline-functionalized oxindole (Scheme 1). Recently, *N*-aryl acrylamides have proven to be efficient radical acceptors,[7] and it was expected that the intermolecular radical addition in our synthetic design would proceed as well.

Pyrazoline derivatives are known to possess potent biological activities, including antiproliferative, antimalarial, and antibacterial activities.[8] On the other side, oxindoles are important heterocyclic scaffolds that exist in a wide range of natural products, pharmaceuticals, and bioactive molecules.[9] Accordingly, these two classes of compounds have attracted much interest from synthetic and pharmaceutical chemists. In this context, the present protocol affords an efficient method for the synthesis of structurally novel pyrazoline-functionalized oxindoles, which possess latent biochemical and pharmaceutical properties as well as a tandem process for the intra/intermolecular C−N/C−C/C−C bond formation involving both activated and unactivated alkenes.

Scheme 1. Strategy for the Hydrazonyl Radical Participated Cascade Cyclization/Addition/Cyclization



To test the assumption, the reaction of *N*-methyl-*N*-phenyl methacrylamide (**1a**, 0.5 mmol) with *N*-phenyl-β,γ-unsaturated hydrazone (**2a**, 1.0 mmol) under oxidative conditions was chosen as a model reaction for the optimization investigation (Table 1). First, TBHP (*tert*-butyl hydroperoxide, 70% aqueous) was tested as the oxidant, but hydrazone **1a** was hydrolyzed to the corresponding ketone with the desired product **3a** undetected (Table 1, entry 1). Next, when TBHP (5−6 M in decane) was used in the reaction, the desired product **3a** was obtained in 34% yield (Table 1, entry 2). Remarkably, treatment of **1a** and **2a** with DTBP (di-*tert*-butyl peroxide) led to the product **3a** in 71% yield (Table 1, entry 3). The use of other oxidants such as TBPB (*tert*-butyl peroxybenzoate), BPO (benzoyl peroxide), and AIBN

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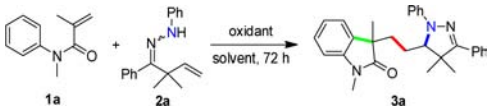
Table 1. Optimization for the Tandem Reaction[a]



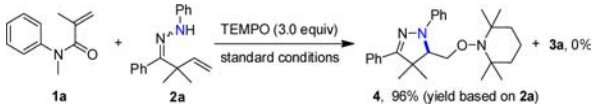
entry	oxidant (equiv)	solvent	t (°C)	%, yield[b]
1	TBHP[c] (4.0)	neat	100	trace
2	TBHP[d] (4.0)	neat	100	34
3	DTBP (4.0)	neat	100	71
4	TBPB (4.0)	neat	100	45
5	BPO (4.0)	toluene	100	trace
6	AIBN (4.0)	toluene	100	16
7	**DTBP (6.5)**	**neat**	**100**	**88**
8[e]	DTBP (6.5)	neat	120	67

[a]Reaction conditions: a mixture of **1a** (0.5 mmol, 1 equiv), **2a** (1.0 mmol, 2 equiv), and solvent (0.5 mL) was stirred under an argon atmosphere. [b]Yield of isolated products. [c]TBHP (70% aqueous). [d]TBHP (5−6 M in decane). [e]After 48 h.

(2,2-azobisisobutyronitrile) did not provide better results (Table 1, entries 4−6). Gratifyingly, with the increase of the usage amount of DTBP to 6.5 equiv, the yield of **3a** was increased to 88% (Table 1, entry 7). In order to shorten the reaction time, we attempted to heat the reaction system up to 120 °C, but the result was rather disappointing (Table 1, entry 8).

To identify that the generation of hydrazonyl radical was the initial step, a control experiment was carried out as shown in Scheme 2. When the carbon-centered radical scavenger TEMPO

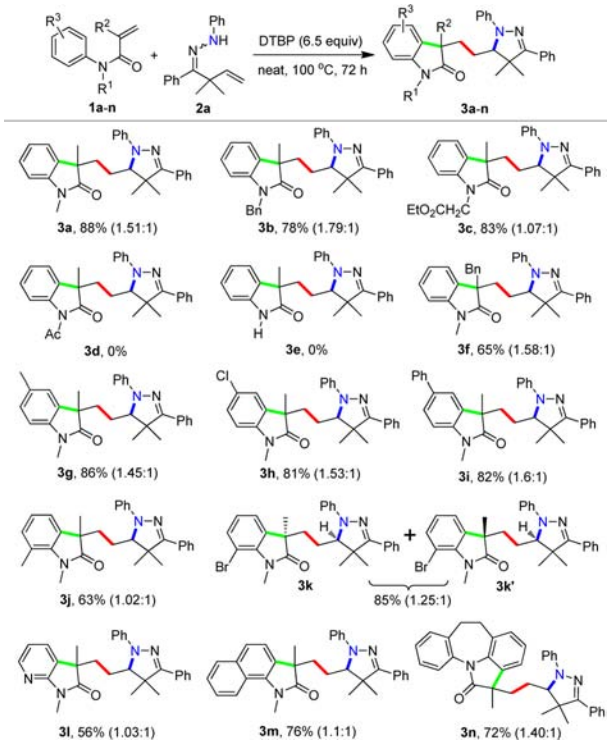
Scheme 2. Control Experiment



(2,2,6,6-tetramethylpiperidin-1-oxyl) was added in the reaction under the standard reaction conditions, the desired compound **3a** was not detected but the pyrazoline **4**, which was obviously yielded from the trapping of the C-centered radical derived from the hydrazonyl radical fast 5-*exo*-*trig* cyclization by TEMPO, was formed as the sole product in 96% yield. This observation demonstrated clearly that the initiation step is the generation of the hydrazonyl radical.

With the optimal conditions in hand (Table 1, entry 7), the scope of *N*-aryl acrylamides **1** was tested to react with *N*-phenyl-*β*,*γ*-unsaturated hydrazone **2a**, and the results are listed in Scheme 3. Acrylamides with various *N*-protecting groups, such as *N*-Me, *N*-Bn, and *N*-CH_2COOEt, were tolerated well to afford the desired pyrrazoline-functionalized oxindoles in good yield (**3a**−**c**). However, the *N*-acetyl and *N*-unprotected acrylamides did not work (**3d**−**e**). When the substrate bearing Bn (benzyl group) at the 2-position of the acrylamide moiety participated in the tandem reaction, the corresponding product **3f** was also gained in 65% yield. Then, the substituent effects on the aromatic ring of *N*-aryl acrylamides were also studied. Screening showed that several substituents, such as *p*-Me, *p*-Cl, *p*-Ph, *o*-Me, and *o*-Br groups, were well tolerated under the optimal conditions and delivered the corresponding products in good to excellent yields (**3g**−**k**). Significantly, in the case of *o*-Br substituted *N*-methyl-*N*-phenyl methacrylamide, the acquired diastereoisomers could be separated as **3k** and **3k**′ in a ratio of 1.25:1. The structure of **3k** was confirmed by a single-crystal X-ray diffraction study (Figure

Scheme 3. Scope of *N*-Aryl Acrylamides[a,b,c]



[a]Reaction conditions: a mixture of **1** (0.5 mmol, 1 equiv), **2a** (1.0 mmol, 2 equiv), and DTBP (3.25 mmol, 6.5 equiv) was stirred at 100 °C under argon in neat for 72 h. [b]Yield of isolated products. [c]Ratios in parentheses indicate the diastereomers, and they were determined by ^{1}H NMR spectroscopy.

1). When *N*-methyl methacrylamides bearing pyridine and naphthalene were involved in the reaction, the expected products

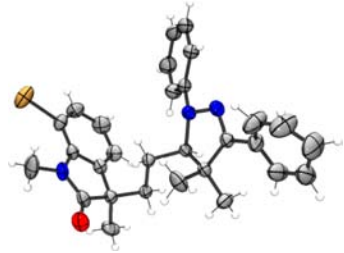


Figure 1. X-ray structure of **3k** (thermals ellipsoids are shown with 30% probability).

3l and **3m** were afforded in 56% and 76% yield, respectively. Notably, a larger tetracyclic oxindole derivative **3n** was also successfully prepared in 72% yield with this protocol.

Having successfully achieved the tandem reaction with *N*-aryl acrylamides, we then shifted our attention to explore the scope of *β*,*γ*-unsaturated ketohydrazones (Scheme 4). *N*-Phenyl with a range of electronic properties substituted *β*,*γ*-unsaturated ketohydrazones all proceeded well in the reaction to yield the desired pyrazoline-functionalized oxidoles in excellent yields (**3o**−**r**). In addition, *N*-alkyl substituted ketohydrazone was also tolerated in the reaction and gave the corresponding product **3s** in 55% yield. However, *N*-acetyl and *N*-tosyl substituted ketohydrazones were inert in the reaction probably due to their strong N−H bond (**3t**−**u**). *β*,*γ*-Unsaturated *N*-phenyl

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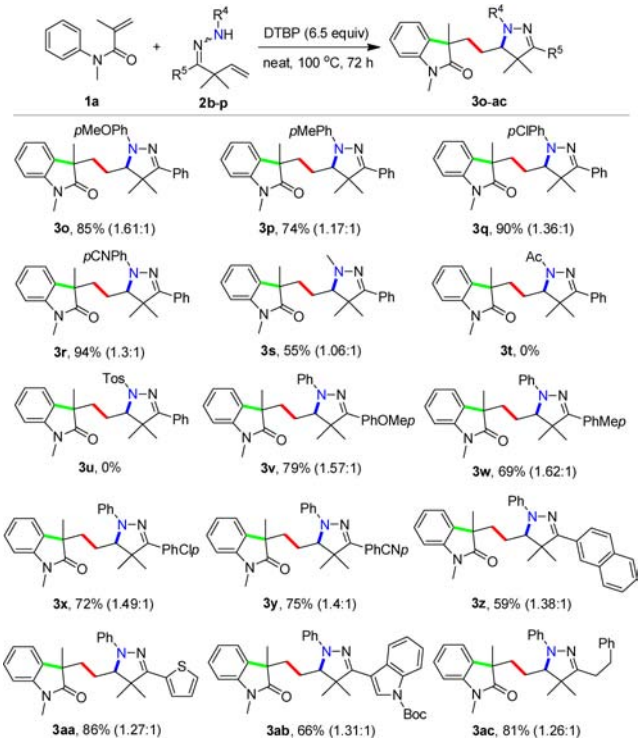
Scheme 4. Scope of β,γ-Unsaturated Ketohydrazones[a,b,c]

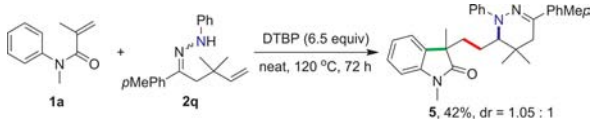


[a]Reaction conditions: a mixture of **1a** (0.5 mmol, 1 equiv), **2** (1.0 mmol, 2 equiv), and DTBP (3.25 mmol, 6.5 equiv) was stirred at 100 °C under argon in neat for 72 h. [b]Yield of isolated products. [c]Ratios in parentheses indicate the diastereomers, and they were determined by ^{1}H NMR spectroscopy.

ketohydrazones bearing aryls such as substituted phenyls, naphthyl, thiophene, and indole participated smoothly in the tandem reaction as well, giving rise to the corresponding pyrazoline-functionalized oxindoles in good to excellent yields (**3v**–**ab**). Moreover, alkyl incorporated *N*-phenyl ketohydrazone was transformed to the desired product **3ac** in 81% yield.

In addition, when γ,δ-unsaturated hydrazone **2q** was reacted with **1a**, the tetrahydropyridazine-functionalized oxindoles **5** was obtained in 42% yield (Scheme 5). This observation is consistent

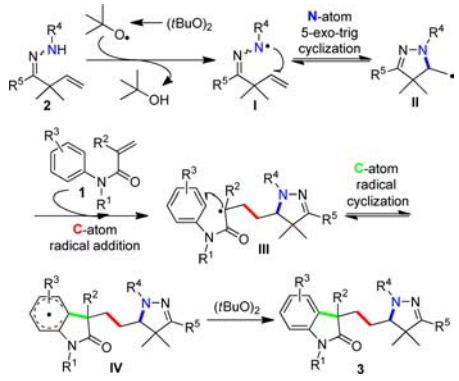
Scheme 5. γ,δ-Unsaturated Ketohydrazone-Participated Tandem Reaction with *N*-Phenylmethacrylamide



with our previous findings that γ,δ-unsaturated hydrazone-derived hydrazonyl radicals are suitable for the N atom 6-*exo*-*trig* cyclization; therefore, the present protocol is also convenient to synthesize tetrahydropyridazine-functionalized oxindole derivatives.

To account for the aforementioned results, a mechanism was proposed as shown in Scheme 6. DTBP first decomposes to produce *t*-BuO radical under the condition of heating; the latter initiates hydrazone **2** to the corresponding hydrazonyl radical **I** via a HAT (hydrogen atom transfer) process. The hydrazonyl radical **I** subsequently undergoes fast 5-*exo*-*trig* cyclization to yield the corresponding C-centered radical **II**. Intermolecular

Scheme 6. Plausible Mechanism for Hydrazonyl Radical-Participated Tandem Reaction



addition of the C-centered radical **II** to the carbon−carbon double bond of *N*-aryl acrylamide **1** produces the deuterogenic C-centered radical adduct **III**, which ulteriorly cyclizes to the adjacent phenyl ring to yield the cyclohexadienyl radical **IV**. Finally, further oxidative aromatization of the cyclohexadienyl radical **IV** by DTBP gives the desired product **3**.

In conclusion, a novel and efficient metal- as well solvent-free protocol has been developed for the synthesis of structurally novel pyrazoline-functionalized oxindoles via tandem cyclization/addition/cyclization sequence using β,γ-unsaturated hydrazones and *N*-aryl acrylamides as the easily prepared substrates and DTBP as the commercially available oxidant. To the best of our knowledge, this study represents the first example of using DTBP as the oxidant for the initiation of hydrazonyl radical as well as the first example of hydrazonyl radical-participated one-pot tandem intra/intermolecular C−N/C−C/C−C bond formation involving both activated and unactivated alkenes. Further studies on the hydrazonyl radical promoted reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03003.

Detailed experimental procedures and spectral data for all products (PDF)
Compound **3k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanb@lzu.edu.cn

Notes

The authors declare no competing financial interest.

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