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3-Alkylperoxy-3-cyano-oxindoles from 2-Cyano-2-diazo-*N*-phenyl-acetamides via Cyclizing Carbene Insertion and Subsequent Radical Oxidation

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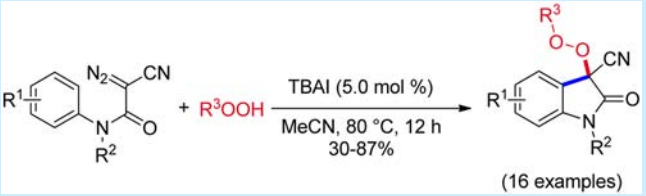
Supporting Information

ABSTRACT: A transition-metal-free one-pot sequence for the synthesis of 3-peroxy-substituted oxindoles from readily prepared 2-cyano-2-diazo-acetamides is reported. The two-step tandem process includes a highly efficient thermal intramolecular C−H-carbene insertion followed by a tetrabutylammonium iodide (TBAI) catalyzed radical C3-peroxy-functionalization. The protocol provides easy access to a new class of 3-cyano-3-peroxy-disubstituted oxindoles. Useful transformations to amides and alcohols are demonstrated.

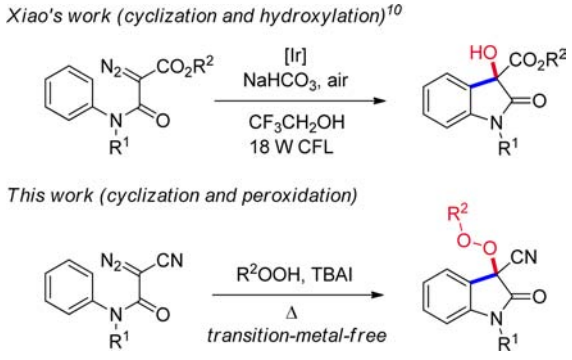


The oxindole core is an important substructure that can be found in various indoline alkaloids.[1] In particular C3-substituted oxindoles show unique biological activity, and they can be identified as a recurring motif in many natural products[2] and pharmaceutical compounds.[3] Therefore, several methods for the synthesis of C3-functionalized oxindoles have been developed over the years.[4] However, peroxy-substituted oxindoles have not been well investigated to date. This is surprising since the peroxo entity is also observed in natural products[5] and has gained interest in pharmaceutical research.[6] Therefore, the development of efficient methods for the synthesis of peroxy-substituted oxindoles is important in order to fully exploit their biological potential.

3-Peroxy-oxindoles have been prepared by organo[7]- or Ni[8]-catalyzed addition of alkyl hydroperoxides to isatin-derived ketimines to give the corresponding 3-amino-3-peroxy-oxindoles. Furthermore, hydroperoxide intermediates are generated during pentanidium catalyzed α-hydroxylation of α-substituted oxindoles.[9] In all these processes the synthesis starts with preformed oxindole core structures. Recently, Xiao and co-workers reported the synthesis of 3-hydroxy-oxindoles from α-diazoamides via a photoredox-catalyzed tandem process (Scheme 1).[10] This sequence comprises C−C bond formation to give intermediate oxindoles which in turn become oxidized to 3-hydroperoxy-oxindoles. Reductive O−O bond cleavage eventually leads to 3-hydroxy-oxindoles (Scheme 1). However, methods allowing for direct preparation of 3-peroxy-substituted oxindoles from α-diazoamides are currently unknown. Also considering the growing importance of step economy[11] in synthesis we report herein a transition-metal-free method for direct preparation of 3-peroxy-oxindoles from readily accessible α-cyano-α-diazo-amides.

The oxindole framework is often constructed via intramolecular C−H-carbene insertion reactions of α-diazo compounds[12] by using transition metals such as Rh,[13] Ru,[14] and Ag[15] as catalysts. We therefore decided to use 2-cyano-2-diazoacetamides as starting materials and *t*-BuOOH (TBHP) in combination with Bu_4NI (TBAI)[16] for peroxidation and attempted to develop a sequence comprising a transition-metal-free carbene insertion reaction[17] with subsequent metal-free oxidation.[18]

Scheme 1. Approaches to C3-Disubstituted Oxindoles



2-Cyano-2-diazo-*N*-methyl-*N*-(*p*-tolyl)acetamide (**1a**) was chosen as a model substrate for optimization studies (Table 1). Amide **1a** and all other 2-cyano-2-diazo-acetamides were readily accessed in two steps by Steglich esterification[19] and subsequent Regitz diazotransfer.[20] Reactions were conducted with TBHP (5.0 equiv) in the presence of TBAI (5.0 mol %) at 60 °C for 48 h, and commonly used solvents were screened first (Table 1, entries 1−3). Pleasingly, 56% of the targeted **2a** was obtained upon running the cascade in benzene (Table 1, entry 1). In dioxane a complex reaction mixture resulted and only a trace amount of **2a** was identified (Table 1, entry 2). The best

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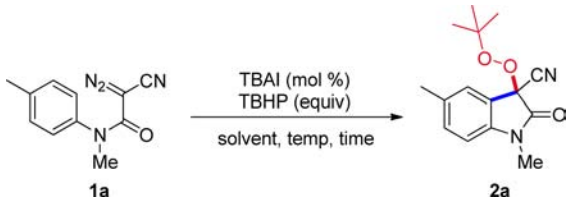
Table 1. Reaction Optimization with 1a as a Substrate[a]



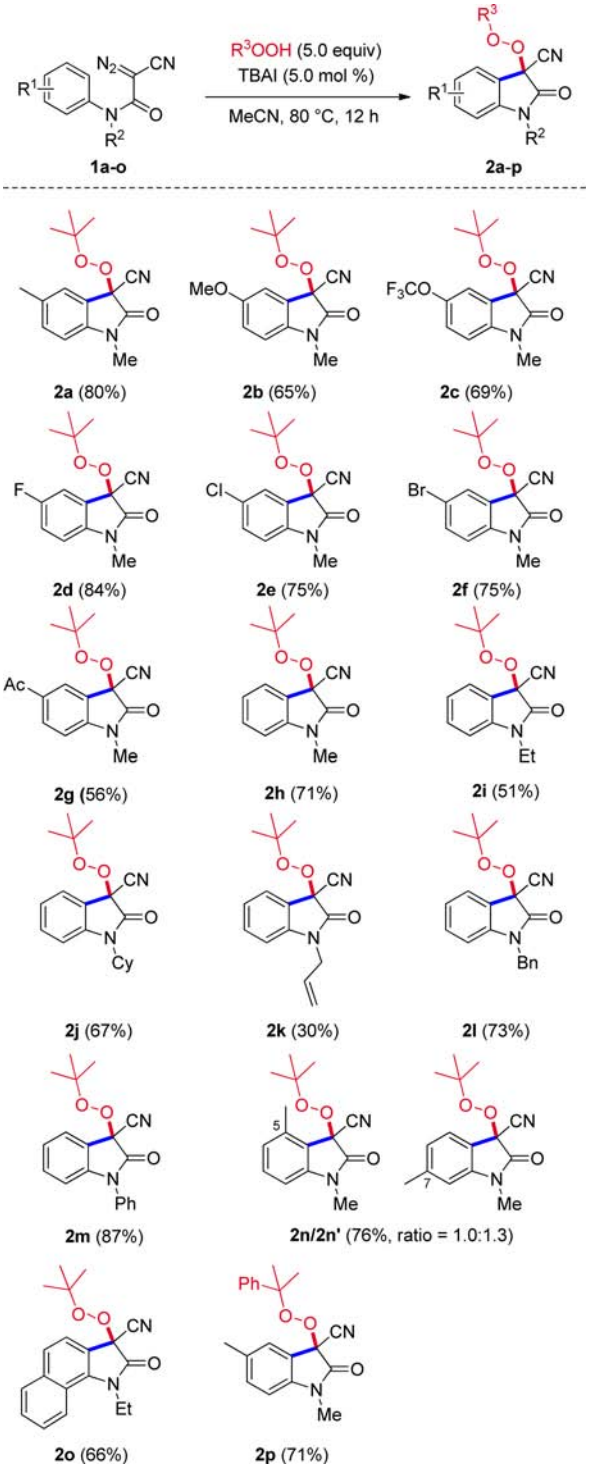
entry	TBHP (equiv)	TBAI (mol %)	solvent	temp (°C)	time (h)	yield (%)
1	5.0	5.0	benzene	60	48	56[c]
2	5.0	5.0	dioxane	60	48	trace
3	5.0	5.0	MeCN	60	48	70[b]
4	5.0	5.0	MeCN	90	24	70[c]
5	**5.0**	**5.0**	**MeCN**	**80**	**12**	**80**[b]
6	5.0	10.0	MeCN	80	12	66[b]
7	5.0	1.0	MeCN	80	12	67[b]
8	5.0	–	MeCN	80	12	39[b]
9	10.0	5.0	MeCN	80	12	74[b]
10	2.5	5.0	MeCN	80	12	61[b]

[a]Reactions were conducted with **1a** (0.25 mmol, 0.25 M). [b]Isolated yield. [c]Yields determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

result in this series was obtained in MeCN, and **2a** was obtained in 70% isolated yield (Table 1, entry 3). The reaction time could be decreased to 24 h by increasing the temperature to 90 °C without diminishing the yield (Table 1, entry 4). The ideal reaction temperature was found to be 80 °C (12 h), and oxindole **2a** was isolated in 80% yield (Table 1, entry 5). Varying the amount of TBAI did not lead to any further improvement of the yield (Table 1, entries 6 and 7). Notably, conducting the reaction in the absence of TBAI provided **2a** in 39% yield (Table 1, entry 8).[21] Increasing or lowering the amount of oxidant led to lower yields (Table 1, entries 9 and 10).

To document the substrate scope, various 2-cyano-2-diazoacetamides **1a–o** were reacted under optimized conditions (Table 1, entry 5) to the corresponding peroxy-substituted oxindoles **2a–o** (Scheme 2). The effect of the *para*-substituent in the 2-cyano-2-diazo-acetamide was investigated first (**2a–g**). Electronic effects are small, and no real trend was noted. Both electron-donating and -withdrawing substituents were tolerated, and oxindoles **2a–g** were isolated in moderate to good yields (56–84%). We further examined the effect of the N-substituent and tested the ethyl-, cyclohexyl-, allyl-, benzyl-, and phenyl-substituted diazoacetamides **1h–m** along these lines. Except for the N-allylated system **1k**, where oxindole **2k** was isolated in low yield (30%), all other congeners provided the corresponding products **2h–j**, **2l**, and **2m** in good yields. The structure of the *N*-phenyl-substituted-oxindole **2m** was confirmed by X-ray analysis (Figure 1). The *meta*-substituted amide **1n** afforded the cylization/oxidation product as an isomeric mixture (**2n**/**2n**′ = 1.0:1.3) in 76% combined yield. However, the naphthyl derivate **1o** provided the five-membered-ring oxindole **2o** with complete regiocontrol in 66% yield. The six-membered ring product was not observed. Finally, the method was shown to work well with cumyl hydroperoxide in place of TBHP as documented by the successful preparation of oxindole **2p** (71%). Notably, with 2-acetyl-2-diazo-*N*-methyl-*N*-phenyl-acetamide as a substrate, reaction under the optimized conditions delivered *N*-methylisatin in 52% yield.

Scheme 2. Preparation of Various 2-Cyano-2-alkylperoxy-Substituted Oxindoles 2a–p (Isolated Yields)



To shed light on the mechanism of the novel cascade, mechanistic experiments were conducted. Upon heating **1a** in MeCN to 80 °C in the absence of TBHP/TBAI, 2-cyano-oxindole **3a** was obtained in 98% yield (Scheme 3). If **3a** gets exposed to the applied reaction conditions product **2a** was formed in 51% yield. These two experiments indicate that our cascade proceed via initial cyclization to form compounds of type **3** as intermediates followed by TBHP/TBAI-mediated oxidation. We assumed that cyclization occurs via carbene C–

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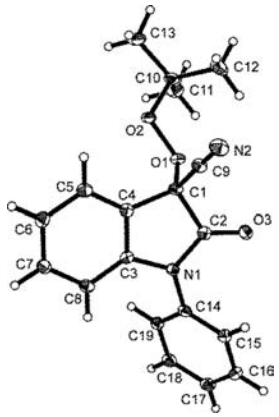
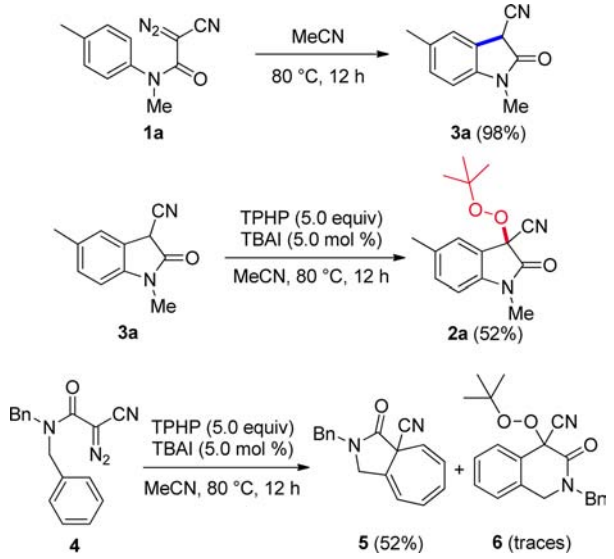


Figure 1. X-ray structure of oxindole **2m** (thermal ellipsoids are shown with 30% probability).

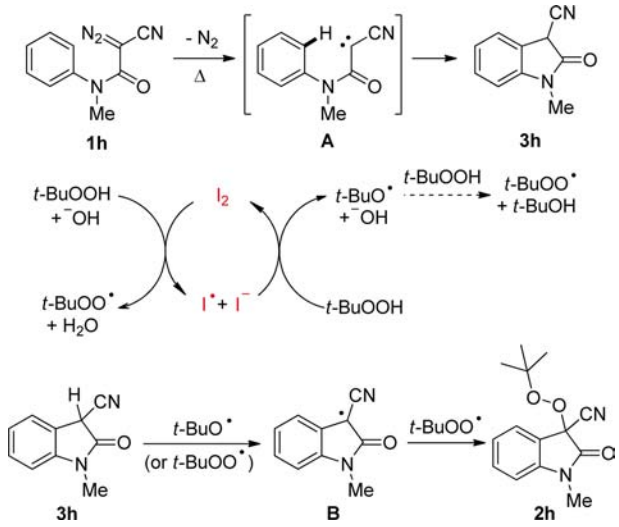
Scheme 3. Mechanistic Studies



H-insertion into the arene and that the carbene is generated thermally from the corresponding α-diazoamide. However, we were surprised that carbene generation in the absence of any transition metal occurs that efficiently at 80 °C.[22] To prove generation of a free carbene under the reaction conditions, we tested dibenzyl substituted diazo amide **4** as a substrate and isolated cycloheptatriene **5** in 52% yield as the major product. Cyclization/oxidation compound **6** was identified in trace amounts. The formation of **5** is the result of a Büchner ring expansion reaction[23] providing strong evidence for the formation of a free carbene under the applied conditions. We therefore disregard C−C bond formation to occur via a homolytic aromatic substitution.[24]

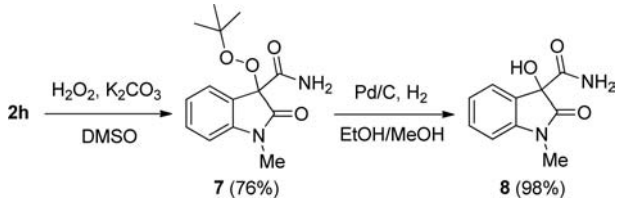
Based on these studies the following mechanism is proposed for the synthesis of peroxy-substituted oxindoles from α-diazoacetamides (Scheme 4). In the first step, carbene **A**, thermally generated from **1h**, undergoes a concerted C−H-carbene insertion to the neighboring arene to give 2-cyano-oxindole **3h**. For the second step we suggest a TBAI catalyzed oxidation process.[25] Electron transfer (ET) from iodide to TBHP generates via a reductive O−O bond cleavage an iodine radical, a *tert*-butoxyl radical, and the hydoxyl anion. The *tert*-butoxyl radical then abstracts the α-carbonyl H atom of intermediate **3h** forming *t*-BuOH and C-radical **B**. Alternatively, the *tert*-butoxyl radical might react with TBHP via H-abstraction to give *t*-BuOH and the *tert*-butylperoxyl radical, which itself can abstract the α-H atom in **3h** to give **B**. Iodine (I_2), formed upon iodine radical dimerization, gets reductively cleaved by the TBHP anion, thereby generating a longer lived *tert*-butylperoxyl radical, an iodine radical, and iodide anion. Hence, we assume that iodide acts as a catalyst in this oxidation process, as suggested before.[16b] Steered by the persistent radical effect,[26] the longer lived *tert*-butylperoxyl radical eventually undergoes selective cross-coupling with radical **B** to give the isolated product **2h**.

Scheme 4. Proposed Mechanism



Finally, to document the potential of the method for the preparation of α-substituted-α-hydroxy-oxindoles, we planned to reduce the O−O bond in **2h**. However, all of our attempts failed. Upon reduction of **2h** the intermediate α-cyano-α-hydroxy-indole underwent, under the tested conditions, fast HCN elimination to give *N*-methyl isatin. Depending on the reduction conditions isatin was then further reduced to α-hydroxy-*N*-methyl-oxindole lacking the α-cyano substituent. Therefore, **2h** was first converted to the primary amide **7** by treatment with H_2O_2 under basic conditions (76%, Scheme 5). Reduction of the peroxide with H_2 in the presence of Pd on charcoal as a catalyst gave 3-hydroxy-oxindole **8** in excellent yield (98%).

Scheme 5. Preparation of an α-Hydroxyoxindole



In summary, a novel class of α-peroxy-substituted oxindoles has been synthesized via a transition-metal-free one-pot sequence starting from readily accessible 2-cyano-2-diazo-acetamides. Reactions proceeded via initial carbene C−H insertion to construct the oxindole core, followed by a radical α-peroxidation with alkyl hydroperoxides and TBAI as a catalyst. The nitrile functionality in the α-peroxy-substituted oxindoles can be hydrolyzed to give the corresponding peroxy-

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amides, and subsequent reductive O−O bond cleavage leads to α-hydroxy-oxindoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00367.

Experimental details, characterization data for the products (PDF)

Supplementary crystallographic data (CCDC 1451727) (CIF)

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Notes

The authors declare no competing financial interest.

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