

3-Alkylperoxy-3-cyano-oxindoles from 2-Cyano-2-diazo-N-phenylacetamides 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-peroxyfunctionalization. The protocol provides easy access to a new class of 3-cyano-3-peroxy-disubstituted oxindoles. Useful transformations to amides and alcohols are demonstrated.

T he oxindole core is an important substructure that can be found in various indoline alkaloids.¹ In particular C3substituted oxindoles show unique biological activity, and they can be identified as a recurring motif in many natural products² 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 products⁵ 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 organo⁷- or Ni⁸catalyzed addition of alkyl hydroperoxides to isatin-derived ketimines to give the corresponding 3-amino-3-peroxyoxindoles. 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 coworkers 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 economy¹¹ 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 compouds¹² by using transition metals such as Rh,¹³ Ru,¹⁴



Scheme 1. Approaches to C3-Disubstituted Oxindoles

Xiao's work (cyclization and hydroxylation)¹⁰



and Ag^{15} as catalysts. We therefore decided to use 2-cyano-2diazoacetamides as starting materials and *t*-BuOOH (TBHP) in combination with Bu₄NI (TBAI)¹⁶ for peroxidation and attempted to develop a sequence comprising a transitionmetal-free carbene insertion reaction¹⁷ with subsequent metalfree oxidation.¹⁸

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 esterification¹⁹ 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

	N ₂ N Me 1a	CN TE TE O solve	TBAI (mol %) TBHP (equiv) solvent, temp, time		CN CN N Me 2a		
entry	TBHP (equiv)	TBAI (mol %)	solvent	temp (°C)	time (h)	yield (%)	
1	5.0	5.0	benzene	60	48	56 [°]	
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 ⁶	
10	2.5	5.0	MeCN	80	12	61 ^b	

"Reactions were conducted with 1a (0.25 mmol, 0.25 M). ^bIsolated yield. ^cYields determined by ¹H 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 phenylsubstituted 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 10 provided the five-membered-ring oxindole 20 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-phenylacetamide as a substrate, reaction under the optimized conditions delivered N-methylisatin in 52% yield.



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-cyanooxindole 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–

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



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 reaction²³ 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–Hcarbene insertion to the neighboring arene to give 2-cyanooxindole **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**. Alter-

Scheme 4. Proposed Mechanism



natively, the *tert*-butoxyl radical might react with TBHP via Habstraction to give *t*-BuOH and the *tert*-butylperoxyl radical, which itself can abstract the α -H atom in **3h** to give **B**. Iodine (I₂), 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**.

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 H₂O₂ under basic conditions (76%, Scheme 5). Reduction of the peroxide with H₂ 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-diazoacetamides. 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 peroxyamides, 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.or-glett.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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