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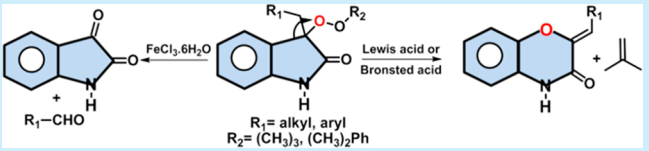
The Rearrangement of Peroxides for the Construction of Fluorophoric 1,4-Benzoxazin-3-one Derivatives

Moreshwar B. Chaudhari, Atul Chaudhary, Vishnupriya Kumar, and Boopathy Gnanaprakasam*

Department of Chemistry, Indian Institute of Science Education and Research, Pune-411008, Maharashtra, India

Supporting Information

ABSTRACT: An unprecedented skeletal rearrangement of 3-(*tert*-butylperoxy)indolin-2-one using a tin catalyst has been developed. This rearrangement is highly selective to afford a series of fluorophoric (*Z*)-2-arylidene and alkylidene-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives in good to excellent yield. In contrast with $Sn(OTf)_2$, the reaction of 3-(*tert*-butylperoxy)indolin-2-one derivatives with $FeCl_3$ afforded the Hock fragmentation product via C−C bond cleavage.



The peroxidation and related reactions have pivotal importance in the oxidation processes of bioconjugates and drug discovery. The organic peroxide serves as an important intermediate in several oxidative transformations.[1a−e] The synthesis, isolation, and storage of peroxides suffer minor difficulties, because of weak oxygen−oxygen bonds (ΔH°_{298} = 158−194 kJ mol^{-1}).[2] The low bond energy of a peroxide make them intriguing scaffolds for several transformations. The rearrangement of organic peroxide constitutes a modification in the starting molecule to produce an isomeric or nonisomeric compound with or without peroxy groups. Synthetically, the cumene process or Hock process is the basis of synthesizing phenol from cumene hydroperoxide and is one of the remarkable examples for rearrangement of organic peroxide, which can be attributed to the acidic source (Figure 1).[3] In biochemistry, lipid peroxidation is an important research area; as a result, attracting scientific community from across many disciplines. The naturally occurring oxylipins constitute a family of oxygenated natural products that are ubiquitous in plants, animals, and fungi. Enzymatically, in oxylipin metabolism, hydroperoxide lyase (HPL) converts fatty acid hydroperoxides to hemiacetal derivatives via Hock-type rearrangement that spontaneously decomposes to the aldehydes (Figure 1).[4a−e] In past decades, varieties of named[5] and unnamed[6] rearrangement of organic peroxides are documented in the literature. However, the migration of aryl or alkyl group toward electron-deficient oxygen atom has been widely studied for the Baeyer−Villiger oxidation[7a−d,e,f] and Criegee solvolysis of peresters.[8a−d]

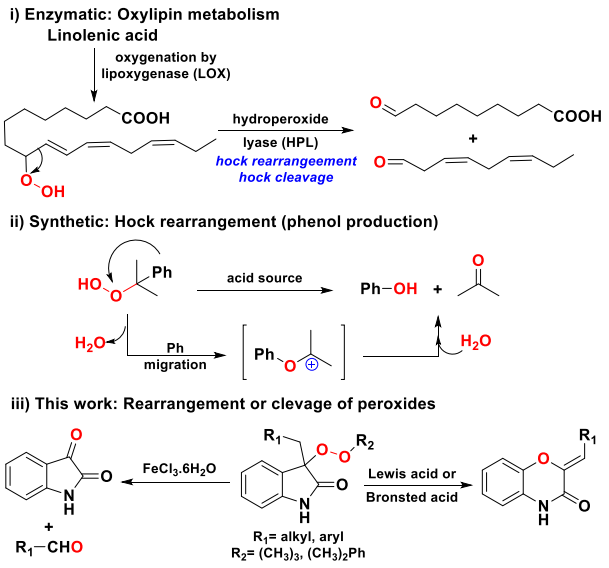


Figure 1. State of the art on the rearrangement of peroxides

The syntheses of nitrogen-containing heterocyclic compounds are important in all facets of chemistry. In particular, the chemistry of 2-oxindole derivatives is well-studied, because of their omnipresence in pharmaceuticals and natural products. However, maneuvering for the ring-expansion of 2-oxindole derivatives is an enticing paradigm in organic synthesis. Interestingly, the base-mediated skeletal rearrangement of peroxyoxindole was reported by Stoltz and co-workers.[9] The 1,4-benzoxazin-3-one derivatives exemplify a class of important compounds, which exhibits the biological properties such as CNS depressant,[10] antiproliferative,[11] neuroprotective agents.[12] Recently, Sharma and co-workers reported the Pd-catalyzed synthesis of 1,4-benzoxazin-3-one derivatives by employing an Ugi adduct as a precursor.[13] The unique structure and properties of 1,4-benzoxazin-3-ones gave us an inducement to develop an operationally simple and novel pathway for their synthesis.

Herein, we report a Lewis acid, $Sn(OTf)_2$ or Brønsted acid-mediated activation of 3-peroxy-2-oxindoles and its rearrangement to 1,4-benzoxazin-3-one with the liberation of isobutylene. The expansion of the ring was triggered by the C3−C4 carbon shift of 2-oxindole bond toward the electro-

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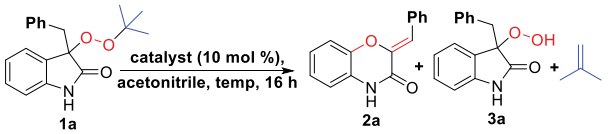
philic oxygen on the peroxide functionality. Moreover, we have demonstrated that the 3-peroxy-2-oxindoles could be cleaved via Hock rearrangement in the presence of $FeCl_3$ to yield isatin and aldehyde (Figure 1). Such types of cleavage reactions can be employed as a probe to determine homolytic versus heterolytic cleavage.[14]

A series of Lewis acids were tested for the rearrangement of **1a** to get the best-optimized condition (Table 1). We

Table 1. Optimization for the Rearrangement of Peroxide[a]



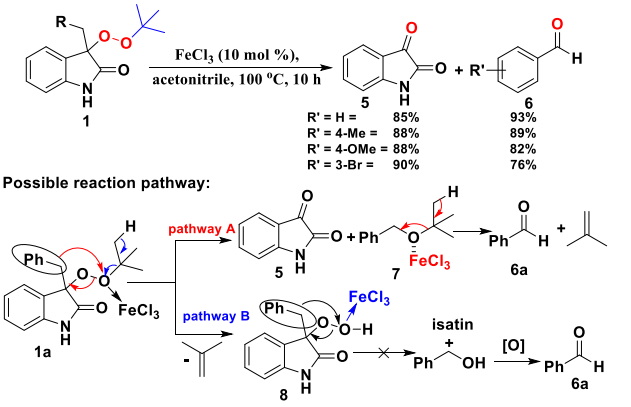
entry	catalyst[b]	temp [°C]	yield **2a**:**3a** [%]
1	none	rt	no reaction
2	none	100	no reaction
3	$Sc(OTf)_3$	rt	00:52
4	$Sc(OTf)_3$	100	40:49
5	Ag(OTf)	100	no reaction
6	$Sn(OTf)_{2-}$	rt	00:57
7	$Sn(OTf)_2$	60	00:60
8	$Sn(OTf)_2$	100	90:00
9	$BF_3.OEt_2$	100	30:63
10	$Cu(OTf)_2$	100	28:51
11[c]	Amberlyst-15	100	31:39
12[d]	Amberlyst-15	100	87:00
13[e]	Amberlyst-15	100	81:10

[a]Reaction conditions: 0.25 mmol (**1a**), catalyst (10 mol %) in a 2 mL acetonitrile was heated at a specified temperature for 16 h in a sealed tube. 0.25 mmol or 78 mg of substrate (**1a**). [b]Catalyst amount = 10 mol %. [c]26 mg. [d]156 mg. [e]78 mg of Amberlyst-15 was used (w/w substrate to Amberlyst-15 ratio is taken). Amberlyst-15 (Dry) form is used. The mentioned yields are isolated yields.

commenced our investigation with the 3-benzyl-3-(*tert*-butylperoxy)indolin-2-one **1a** as a model molecule for the rearrangement. In control experiments, **1a** in acetonitrile (MeCN) was stirred at room temperature and 100 °C in the absence of an acid source, which did not provide any product (Table 1, entries 1 and 2). Next, in the presence of 10 mol % $Sc(OTf)_3$, we observed only the removal of the *tert*-butyl group from **1a** to afford hydroperoxy compound **3a** (52%) and no rearranged product **2a** at room temperature (Table 1, entry 3).

However, when increasing the temperature to 100 °C, we observed two products, rearranged **2a** and deprotected **3a** in a 40% and 49% isolated yield, respectively, with the liberation of isobutylene in 16 h (Table 1, entry 4). The structure of the compound was unambiguously characterized by single-crystal X-ray diffraction. Next, the use of Ag(OTf) did not afford any product or byproduct formation (Table 1, entry 5). The copper triflate provided 28% yield of the rearranged product **2a** and 51% yield of the deprotected compound **3a**. Among the different Lewis acids used, $Sn(OTf)_2$ was noticeably better, in terms of selectivity and yield (Table 1, entry 8). To our delight, the rearranged product **2a** was achieved using Brønsted acid, Amberlyst-15 with a comparable yield to that of Lewis acid (Table 1, entry 12). The selection of Amberlyst-15 for the rearrangement is rational, because it is mild, easy to measure, safe to handle, and easily separable at the end of the reaction. Interestingly, in contrast to $Sn(OTf)_2$ when $FeCl_3$ was used as Lewis acid source with **1a**, we observed Hock rearrangement, which results in the formation of isatin **5** and aldehyde **6** (Scheme 1). We proposed that the peroxide **1a** will react via

Scheme 1. $FeCl_3$-Catalyzed Hock Rearrangement of Peroxides[a]



[a]Reaction conditions: 0.25 mmol (**1a**), $FeCl_3{\cdot}6H_2O$ (10 mol %) in 2 mL acetonitrile was heated at 100 °C for 16 h in a sealed tube. The mentioned yields are isolated yields.

Hock rearrangement. The two possible pathways A and B are depicted in Scheme 1. In pathway A, the migration of phenyl group on the oxygen will generate isatin **5** and (*tert*-butoxymethyl)benzene **7**. The isobutylene will serve as a leaving group to afford benzaldehyde **6a** as a cleaved product.[15] However, the existence of pathway B is unlikely, because of the absence of benzyl alcohol in the reaction mixture. Furthermore, to rule out the possibility of pathway B, the reaction of **3a** was performed with $FeCl_3$, which afforded the traces of rearranged product **2a** and not even traces of benzaldehyde **6a** or benzyl alcohol (most of the **3a** was recovered).

With optimized conditions in hand, the scope of Sn-catalyzed and Amberlyst-15 mediated rearrangement was investigated (Scheme 2). The variety of alkyl or benzyl-substituted peroxyoxindoles were subjected for rearrangement reaction. Benzyl groups bearing electron-donating groups afforded the rearranged product (**2a**−**2d**) with good to excellent yield (Scheme 2). Gratifyingly, the reaction of 3-(*tert*-butylperoxy)-3-cyclohexylindolin-2-one and 3-(*tert*-butylperoxy)-3-hexylindolin-2-one afforded **2e** and **2f** in yields of 78% and 75%, respectively, using $Sn(OTf)_2$. However, the use of Amberlyst-15 provided **2e** and **2f** in isolated yields of 82% and 87%, respectively.

In the case of ethyl 2-(3-(*tert*-butylperoxy)-2-oxoindolin-3-yl)acetate instead of rearrangement, only isobutylene removal was observed (Scheme 2, **2g**). In addition, the rearrangement reaction tolerated a wide variety of electron-withdrawing substituents as well to give products (**2h**−**2k**) in very good yield (Scheme 2). The reaction of C3-substituted-6-chloro-2-oxindole derivatives gives a moderate yield of the product **2l** and **2m** (starting material recovered). The low yield of the product is may be due to electronic destabilization by negative inductive effect of the chlorine. Moreover, *N*-protected peroxy compound reacted smoothly to afford rearranged product **2n** in very good yield (Scheme 2).

Furthermore, 3-aryl-3-((2-phenylpropan-2-yl)peroxy)-indolin-2-one derivatives **4** afforded (*Z*)-2-arylidine-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one compound in moderate to good yield with the removal of α-methylstyrene (Scheme 3)

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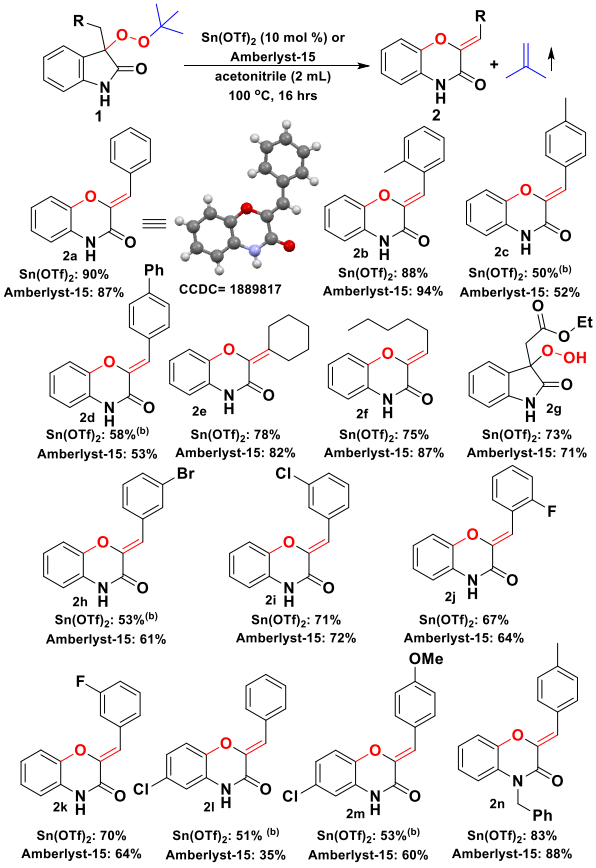
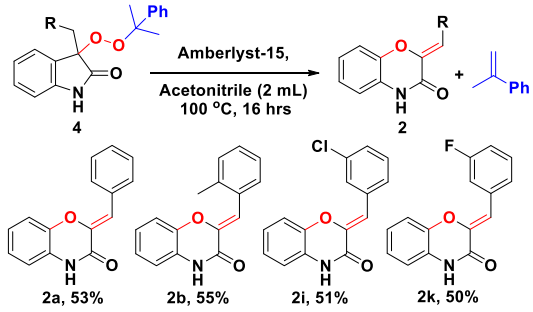
Scheme 2. Substrate Scope for Rearrangement of Peroxide[a]



[a]Reaction conditions: 0.25 mmol (**1a**), $Sn(OTf)_2$ (10 mol %) or Amberlyst-15 (w/w ratio to the substrate) in a 2 mL acetonitrile was heated at 100 °C for 16 h in a sealed tube. [b]20 mol % of $Sn(OTf)_2$ was used and heated for 36 h. The mentioned yields are isolated yields.

Scheme 3. Substrate Scope for the Rearrangement of Peroxide 4 with the Removal of α-Methyl Styrene[a]



[a]Reaction conditions: 0.25 mmol (**4**), Amberlyst-15 (w/w ratio to the substrate) in a 2 mL acetonitrile was heated at 100 °C for 16 h in a sealed tube.

(starting material recovered). To show the utility of the synthesized compounds, we have recorded emission spectra for the selected compounds (Figure 2). The compound displayed a fluorescent emission band at ~430−450 nm (**2k**, 454 nm; **2a**, 452 nm; **2f**, 428 nm) in dimethylsulfoxide (DMSO) solvent. The fluorescent emission band for **2f**, **2a** showed a bathochromic shift (of ~26 nm). This shift is attributed to the presence of extended conjugation in the aromatic rings,

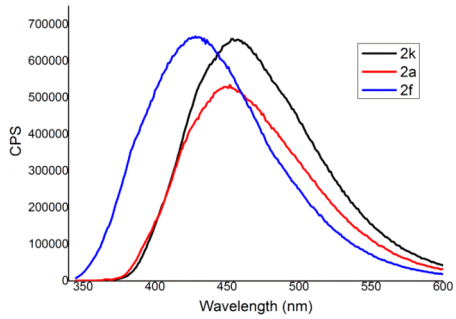
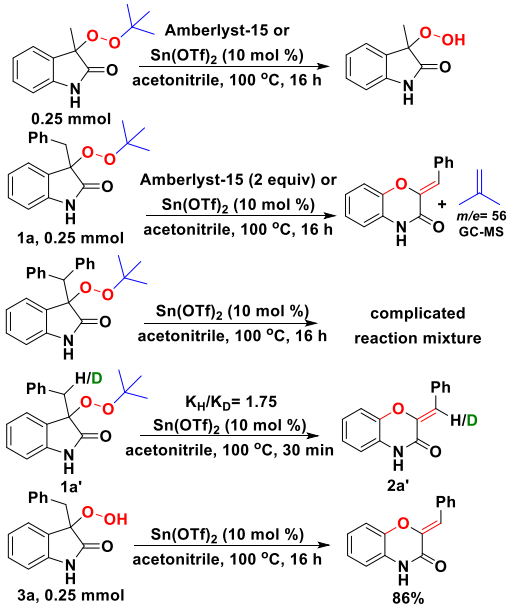


Figure 2. Emission spectra for the selected compounds in DMSO.

compared to **2k**. The prepared compounds could be employed as a fluorescent motif to understand the complex mode of action in the biological processes.[10−12]

To shed light on the reaction parameters, a model reaction was performed with 3-(*tert*-butylperoxy)-3-methylindolin-2-one and 3-hydroperoxy-3-methylindolin-2-one, which does not afford any rearranged product. Next, the reaction of 0.25 mmol of 3-benzhydryl-3-(*tert*-butylperoxy)indolin-2-one with $Sn(OTf)_2$ (10 mol %) provided a complicated reaction mixture (Scheme 4). Above studies indicate the need of the $-(CH_2)-$

Scheme 4. Experiments for Mechanistic Studies



group at the C3-position of peroxyoxindole (except entry **2e**). Next, 3-benzyl-3-(*tert*-butylperoxy)indolin-2-one was subjected to established reaction conditions and a gaseous component of the reaction mixture was analyzed using GC-MS. The GC-MS spectra indicated m/e = 56, which corresponds to the isobutylene gas (see Figure S1 in the Supporting Information (SI)). A parallel reaction was performed with labeled (**1a′**), and unlabeled peroxy (**1a**) compound and a normal primary kinetic isotope effect (KIE) of 1.75 was detected, representing that a H atom transfer is involved in the rate-determining step (Figures S5 and S6 in the SI).[18]

To gain insight into the reaction mechanism, the hydroperoxy compound **3a** was prepared separately and subjected to standard reaction conditions. The expected product **2a** was isolated with a 86% yield which suggests that the reaction

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proceeded via **3a** as an intermediate. Furthermore, the reaction of $Sn(OTf)_2$ and 3-benzyl-3-(*tert*-butylperoxy)indolin-2-one in acetonitrile-d3 was performed in an NMR tube. The notable peaks was observed at 6.82, singlet which belongs to alkene C−H of arylidine product **2a**. Moreover, at 4.66 ppm (septet) and 1.71 (triplet) was also observed, which arises due to the presence of isobutylene (see Figure S2 in the SI).

Based on the experimental results and previous literature reports,[16a,b,17] a plausible reaction mechanism for Sn-catalyzed rearrangement is illustrated in Figure 3. Mechanistically, the

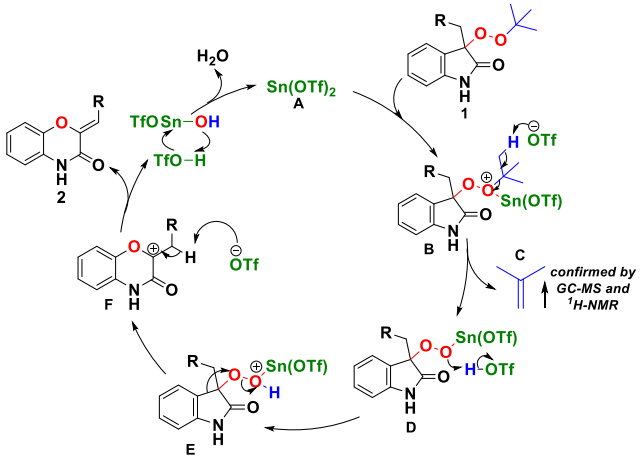

Figure 3. $Sn(OTf)_2$-catalyzed plausible mechanism for the rearrangement.

catalytic cycle initiated by the coordination of peroxy O−O bond of **1** with **A** to give **B**. The deprotonation of **B** commenced by in-situ-generated triflate anion give **D** with the liberation of isobutylene **C** (confirmed by GC-MS and NMR). Following the protonation of SnOTf-chelated oxygen **D** with TfOH, endoperoxide **E** is obtained. A ring expansion is attributed to C3−C4 carbon shift onto oxygen of HO-SnOTf in **E** to give the carbocation **F** and Sn(OH)OTf in a concerted passion. The triflate anion will abstract the proton from **F** to stabilize the carbocation and afford product **2**. Subsequently, catalyst **A** is regenerated by the reaction of Sn(OH)OTf and Tf−OH.

In summary, we have discovered a novel biomimetic cascade rearrangement of 3-peroxy-2-oxindoles that delivers predominantly (*Z*)-2-arylidene or alkylidene-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives in the presence of Lewis/Brønsted acids. Interestingly, in the case of $FeCl_3$, a Hock rearrangement was observed, which can be used to probe the homolytic versus heterolytic cleavage. Based on the experimental results, a plausible mechanism has been proposed, and further detailed investigation for the rearrangement is 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.9b00155.

Experimental procedures and spectroscopic data for the compounds (PDF)

Accession Codes

CCDC 1889817 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gnanaprakasam@iiserpune.ac.in.

ORCID

Boopathy Gnanaprakasam: 0000-0002-3047-9636

Notes

The authors declare no competing financial interest.

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