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Aqueous *tert*-Butyl Hydroperoxide Mediated Regioselective Ring-Opening Reactions of Spiro-aziridine-epoxy Oxindoles: Synthesis of 3-Peroxy-3-substituted Oxindoles and Their Acid-Mediated Rearrangement

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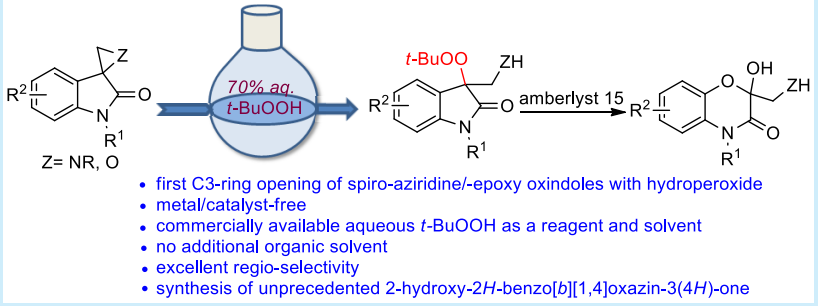
Supporting Information



ABSTRACT: A highly efficient regioselective C3-peroxylation of spiro-aziridine and spiro-epoxy oxindoles has been developed with commercially available 70% aqueous *tert*-butyl hydroperoxide under solvent-free and metal/catalyst-free conditions. The protocol provides an easy access of 3-peroxyoxindoles, which undergo acid-mediated rearrangement to afford unprecedented 2-hydroxy-2-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones. The protocol is also equally effective for the ring opening of simple phenyl aziridine with excellent regio-selectivity.

Synthesis of 3,3-disubstituted oxindoles has been a key goal because of their ubiquitous presence in natural products and drugs.[1] Peroxides, one of the prominent and privileged pharmacophores, exhibit diverse biological and therapeutic activities and constitute the core structural motif of numerous natural products.[2] Furthermore, peroxide-based derivatives have broad applications in medicinal chemistry, like anti-malarial, anthelmintic, antitumor, anticancer, and antiparasite activities.[3] Endoperoxide 1,2,4-trioxane ring containing artemisinin and its derivatives are the drugs of choice to treat multidrug-resistant malaria where the peroxy linkage is responsible for the drug's mechanism of action.[4] The development of synthetic routes to peroxides derivatives of oxindoles is now a focused and active research area.[5]

One of the important challenges of synthesis of peroxide derivatives is to design well-organized substrates that provide structural and functional complexity as well as diversity. Aziridine and epoxide, in particular, spiroaziridines and spiroepoxides, could be versatile substrates for the purpose. A regioselective ring opening of aziridine and epoxide with hydroperoxide would not only generate a wide array of 1,2-peroxyamines and alcohols, respectively, but also can provide an easy and efficient access to 1,4-benzooxazin-3-one derivatives via acid-mediated rearrangement.[6] To the best of our knowledge, there is no report of ring-opening reaction of aziridine with peroxide and only two reports on ring opening of epoxides with an ethereal solution of H_2O_2 in the presence of phosphomolybdic acid and $SnCl_4$.[7] Scalability of hazardous ethereal solution of H_2O_2 is a major concern, particularly in acidic medium. The development of a metal-free, green, and sustainable approach is, therefore, highly desirable for green environments. In this context, we report the first catalyst-free regioselective ring opening of spiro-aziridine/-epoxy oxindoles with aqueous *tert*-butyl hydrogen peroxide (TBHP) without any additional solvent for the efficient synthesis of 3-(*tert*-butylperoxy)-3-(aminomethyl)/(hydroxymethyl)oxindoles. It is also provide an easy and efficient access of unprecedented 2-hydroxy-2-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones by Amberlyst 15 mediated rearrangement.

The regioselective ring-opening reaction of spiro-aziridine- and -epoxyoxindoles at the C3 spiro-center was introduced and explored by our group.[8,9] It is found that spiroaziridine undergoes a smooth ring-opening reaction at the C3-spiro-center mostly under catalyst-free, even "on-water", conditions,[8b−e] whereas spiro-epoxy oxindoles require suitable Lewis/Brønsted acid catalyst for the purpose.[9] On the other hand, catalyst-free water/alcohol mediated reaction of

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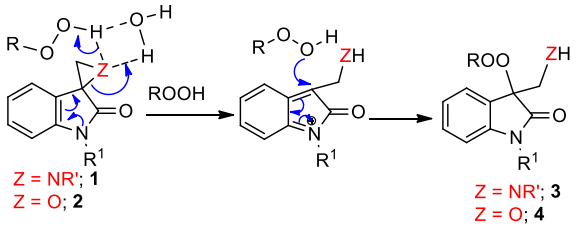
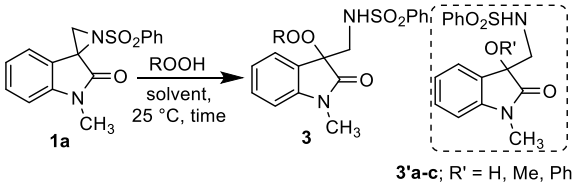
spiroepoxide undergoes ring opening reaction at the terminal site with heteronucleophiles.[10] These led us to envision that both spiro-aziridine and -epoxyoxindoles **1** and **2** would undergo nucleophilic ring-opening reaction at the C3-spiro-center with hydroperoxide (ROOH), where peroxy-hydrogen along with water might activate the substrates through hydrogen bonding (Scheme 1) due to its mild acidity (pK_a ~ 12.7).

Scheme 1. Proposed Ring Opening with ROOH



At the outset of our studies, we used spiro-aziridine oxindole **1a** as the model substrate to test the viability of our hypothesis (Table 1). The ring-opening reaction of spiro-aziridine oxindole **1a** with TBHP (3 equiv; 70% aq solution) was performed without any other solvent. To our delight, the reaction took place in aqueous medium and gave the desired product **3a** in 72% of yield (Table 1; entry 1). With an increased stoichiometry of TBHP (10 equiv), the yield of **3a** raised to 82% (Table 1; entry 2). The influence of temperature on the reaction was also investigated. Decreasing the reaction temperature to 10 °C resulted to a substantial drop in yield (Table 1; entry 3). Addition of extra solvent like methanol decreased the yield of **3a** to 25% and interestingly produced 3-methoxyoxindole as a major byproduct (entry 4). The ring-opening reaction of **1a** with a nonaqueous TBHP (decane solution) was successful only in trifluoroethanol (TFE; entry 5). But in other solvents, it showed either no reaction or poor yield of the desired products (entries 5−7). The presence of Lewis acid catalyst ($Sc(OTf)_3$) was also found to be effective for the ring opening reaction with nonaqueous TBHP (~5.5 M in decane) in CH_2Cl_2 (entry 8). Other hydroperoxide reagents such as 30% aqueous H_2O_2 and cumene hydroperoxide did not produce any desired 3-peroxy compounds (entries 9−11). Hence, commercially available 70% aqueous solution of TBHP was found to be the best reagent as well as solvent for this ring opening reaction. It is to be noted that no regioisomer of the peroxy product was detected by ^{1}H NMR analysis of the crude reaction mixture under optimized conditions.

Table 1. Optimization of Reaction Conditions[a]

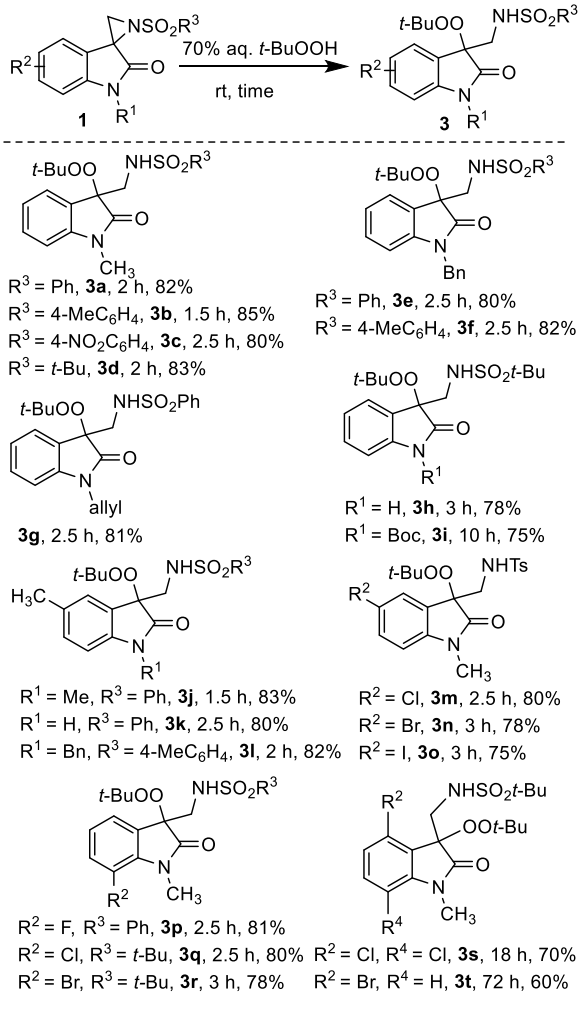


entry	solvent	reagent(s)	time (h)	3/yield[b] (%)	3′/yield[b] (%)
1[c]		aq TBHP	3	**3a**/72	3′/<5
2		**aq TBHP**	**2**	**3a**/**82**	
3[d]	(10 °C)	aq TBHP	6	**3a**/65	
4[e]	MeOH	TBHP	12	**3a**/25	3′/60
5[e]	TFE	TBHP	12	**3a**/78	
6[e]	CH_2Cl_2	TBHP	24	**NR**	
7[e,f]	CH_2Cl_2	TBHP/H_2O	24	**NR**	
8[e,g]	CH_2Cl_2	TBHP/cat.	3	**3a**/75	
9		30% aq H_2O_2	24		3′/80
10[h]		CHP	24		3′/45
11[g,h]	CH_2Cl_2	CHP/cat.	2.5		3′/62

[a]Unless noted, a solution of spiroaziridine **1a** (0.05 g, 0.16 mmol) and aq TBHP (10.0 equiv; 70% in water) in 0.5 mL of solvent (as mentioned in the table) was stirred at rt (25 °C). [b]Isolated yield. [c]3.0 equiv of 70% aq. TBHP. [d]Reaction was performed at 10 °C. [e]TBHP in decane (10.0 equiv, ~ 5.5 M) was used. [f]1.0 equiv of H_2O. [g]$Sc(OTf)_3$ (10 mol %) was used as a catalyst. [h]70% CHP in cumene. TBHP = *tert*-butyl hydroperoxide; CHP = cumene hydroperoxide; NR = no reaction.

With the optimized reaction conditions in hand, the generality of the ring-opening reaction of different spiro-aziridine oxindoles **1a−t** with aqueous TBHP was investigated (Scheme 2). We first examined the effect of *N*-protection of the spiro-aziridine unit with *N*-SO_2Ph, *N*-Ts, *N*-Ns, and *N*-$SO_2{}^t$Bu, and all the congeners provided corresponding products **3a−t** in high yields (60−85%). The effect of *N*-protection of the oxindole unit was found to be minimal on the yield and the reaction time. All of the spiro-aziridines with *N*-Me, *N*-Bn, and *N*-allyl oxindole units underwent smooth ring-

Scheme 2. Synthesis of 3-(Aminomethyl)-3-peroxyoxindoles 3 from Spiro-aziridines 1



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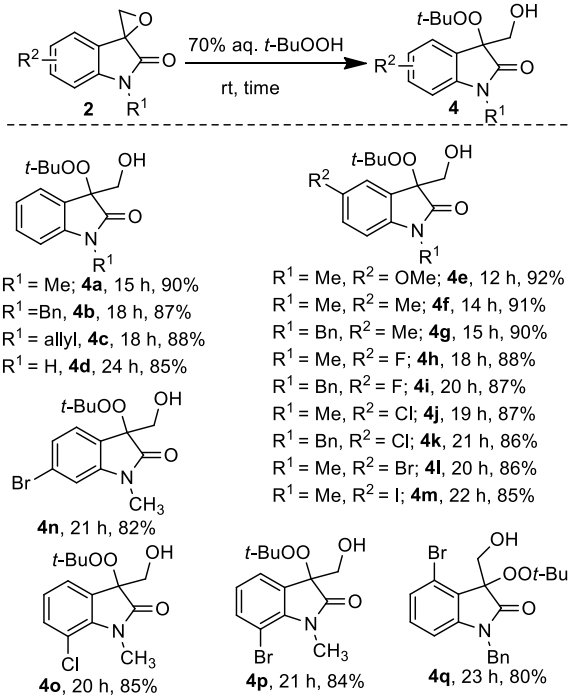
opening reactions and afforded the corresponding desired products **3a−g** with high yields (80−85%). The spiro-aziridine containing *NH*-free oxindole unit reacted efficiently with aq TBHP to give the 3-peroxyoxindole **3h** with 78% of yield. In contrast to our earlier report,[8c−f] the spiro-aziridine **1i** with electron-withdrawing *N*-Boc oxindole underwent smooth reaction under the optimized reaction conditions, only taking a bit more time. A range of electron-donating and -withdrawing substituents at the C4, C5, and C7 positions of the oxindole ring were tested under the reaction conditions. All responded well and gave the corresponding desired products **3j−t** with good to excellent yields. The electronic effect was found to be a minimal, where electron-donating substrates **1j−l** required a shorter time than the electron-withdrawing substrates **1m−r**. The spiroaziridines with halo groups at the C4-position took a longer time for the ring-opening reaction, affording products **3s** and **3t**. As the size increased from Cl to Br, it became very slow and took about 3 days. This might be due to the steric effect at the peri-postion.

Next, we turned our attention to the ring-opening reaction of spiro-epoxy oxindoles **2** under the same conditions (Scheme 3). Unlike earlier works on this chemistry,[9] the C3-ring-

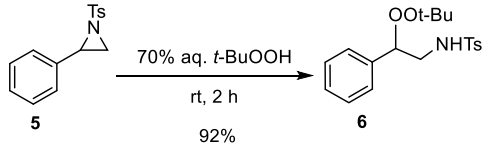
Scheme 3. Synthesis of 3-(Hydroxymethyl)-3-peroxyoxindoles 4 from Spiro-epoxides 2



opening reaction of spiro-epoxy oxindoles **2** with aq *t*-BuOOH proceeded smoothly without any additional Lewis/Brønsted acid. A series of spiro-epoxy oxindoles **2a−q** was investigated under the standardized conditions and all gave high yields of 3-(*tert*-butylperoxy)-3-(hydroxymethyl)indolin-2-ones **4a−q** (80−92%) (Scheme 3). Again, we first checked the substrate scope varying N-protection of oxindole unit. Irrespective of *N*-protection, *N*-Me, *N*-Bn, *N*-allyl, and *N*H-free, all substrates provided the corresponding products **4a−d** with excellent yields (85−90%). The substitution at C4, C5, C6, and C7 of oxindole ring was tested with different electron-donating as well as electron-withdrawing substituents, and all substrates afforded corresponding products **4e−q** with 80−92% yields. In the cases of electron-donating substrates **2e−g** at the C-5 position, the reactions took place smoothly to furnish the products **4e−g** with excellent yield (90−92%). However, when electron-withdrawing substituents at the C4, C5, C6, and C7 positions **2h−2q** were employed, products **4h−q** were obtained with 80−88% yields and took a little more time than the electron-donating substrates **2e−2g**.

Further, the developed protocol was executed for the ring-opening reaction of phenyl aziridine **5** to compare the reactivity pattern with the spiro-aziridine oxindoles **1** (Scheme 4). Interestingly, *N*-Ts phenylaziridine **5** also underwent

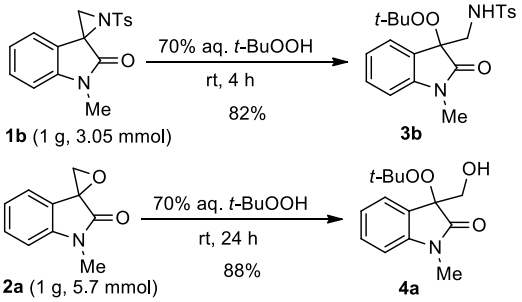
Scheme 4. Aqueous TBHP-Mediated Ring-Opening Reaction of 2-Phenylaziridine 5



smooth reaction with aqueous TBHP and afforded exclusively peroxy product **6** with excellent regioselectivity and yield. The mild acidic nature of aqueous TBHP might similarly activated the aziridine unit, and so no terminal product was detected in the crude reaction mixture.

To manifest the scalability and robustness of the method, the ring-opening reaction of spiro-aziridine and -epoxide were extended up to gram-scale under the optimized conditions (Scheme 5). Both substrates **1b** (1 g, 3.05 mmol) and **2a** (1 g,

Scheme 5. Gram-Scale C3-Peroxylation of 1b and 2a



5.7 mmol) underwent smooth reaction with aqueous TBHP at 25 °C and produced 3-peroxyoxindoles **3b** and **4a** with 82% and 88% yields, respectively, a little lower than the small-scale reactions.

Acid/Lewis acid promoted reaction of 3-*tert*-butylperoxyoxindole was reported to provide either deprotection of the *tert*-butyl group and/or rearrangement reaction, affording 2-alkylidene-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one.[5k,6] In this context, we executed the reaction of **4a** with different acidic conditions (for details, see the SI) with the intention of obtaining 3-hydroperoxy-3-hydroxymethyloxindole **7a**. Among these, the reaction with Amberlyst 15 in acetonitrile was found to be clean and showed the desired mass of *tert*-butyl-deprotected compound **7a** (Scheme 6). Interestingly, rearranged product **8a** with a 2-hydroxy group also has the same mass. However, spectral analysis of the product could not confirm the structure. Thus, the product **7a**/**8a** was reacted with different acetal/carbonyl compounds such as 2,2-

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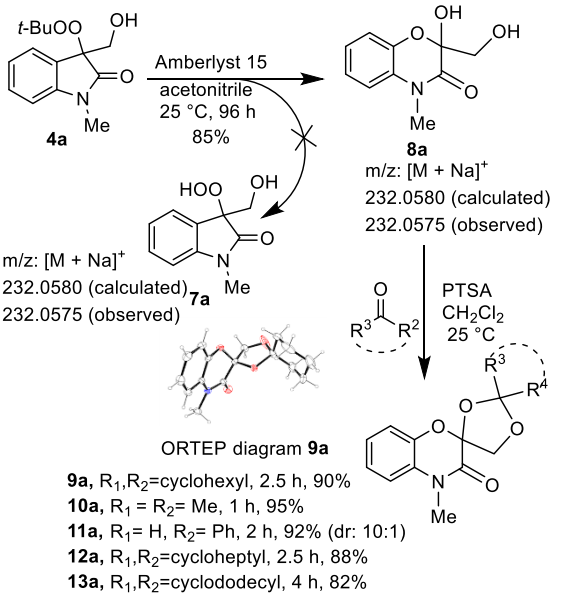
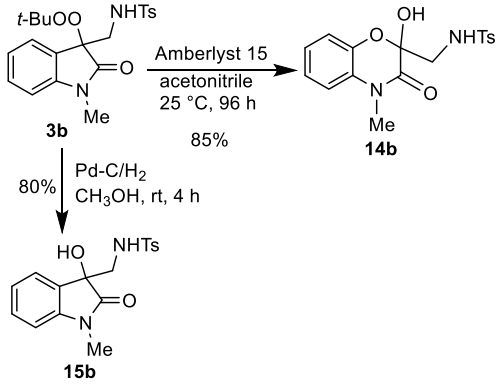
Scheme 6. Acid-Promoted Rearrangement Reaction of 4a



dimethoxypropane, benzaldehyde, cyclohexanone, cycloheptanone, and cyclododecanone in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) in CH_2Cl_2 at rt. Pleasingly, it produced 1,3-dioxalone compounds with desired mass. A single-crystal X-ray analysis of compound **9a** confirmed the structure as a dioxalone derivative of 2-hydroxy-2-hydroxymethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **8a**. The rearrangement reaction of **4a** with Amberlyst 15 producing compound **8a** might follow the similar mechanism as proposed by the Gnanaprakasam group.[6] Here, the presence of additional *β*-hydroxyl group might have restricted the dehydration. It is worth noting that 2-hydroxy-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-one is an important motif present many natural products,[11] and this might be its first chemical synthesis.

3-Peroxyoxindole **3b** was similarly treated with Amberlyst 15 in acetonitrile at rt. It underwent smooth reaction, and with the above analogy the product was assigned as 2-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivative **14b** (Scheme 7). Further removal of the *N*-sulfonoyl group of the **14b** was not successful under different conditions, even changing the reaction sequence. Though a selected *tert*-butyl group could not be removed from the peroxy unit, the -*t*-BuO group of **3b** could be removed by hydrogenation in methanol at rt to afford **15b** with high yield.

Scheme 7. Acid-Promoted Rearrangement Reaction and Pd-Catalyzed Hydrogenation of 3b



In conclusion, a highly efficient regioselective C3-ring-opening reaction of spiro-aziridine and spiro-epoxyoxindoles have been achieved with commercially available 70% aqueous *tert*-butyl hydroperoxide at rt under metal/catalyst-free conditions and without any additional solvent. This protocol provides an easy access of wide variety of 3-peroxy-3-substituted oxindoles. The gram-scale reactions prove its applicability and robustness of the developed protocol. We also developed a Brønsted acid mediated rearrangement reaction of 3-peroxy-2-oxindoles that efficiently provided the first synthesis of 2-hydroxy-2-substituted-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones, important scaffolds present in many natural products. This may unfold a new avenue in 2-hydroxy-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-one-based drug discovery as well as medicinal chemistry research. The catalyst-free aqueous TBHP mediated protocol is equally effective for the simple phenylaziridine. We intend to continue our research efforts toward the ring-opening reaction of spiro-aziridine/epoxyoxindoles with other carbon/hetero nucleophiles in our laboratory. Further detailed investigation for such rearrangement is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04229.

General procedures of C3-peroxylation of **1** and **2**, standardization table for the acid/Lewis acid mediated reaction of **4a**, spectroscopic data of the products **3**, **4**, **6**, **8a**, **9a**−**13a**, **14b**, and **15b**, and copies of their NMR spectra (PDF)

Accession Codes

CCDC 1965971 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.

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Notes

The authors declare no competing financial interest.

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