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Communication

# Oxidative Transformation of Cyclic Ethers/Amines to Lactones/Lactams Using DIB/TBHP Protocol †

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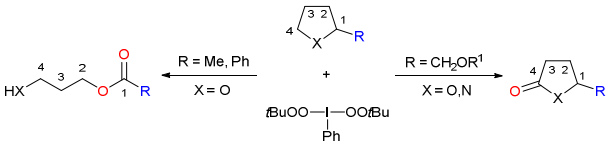
**A novel C-H oxidation of cyclic ethers and amines to the corresponding lactones and lactams was developed using a DIB/TBHP protocol. The reaction is mild and no metallic reagent is involved. In addition, study shows that the electronic properties of the substituents could affect the selectivity of oxidation.**

Lactones and lactams are common structural elements present in numerous biologically activate naturally occurring molecules, for example lignans and rebeccamycin.[1] Owing to their prevalence in natural products, there have been a number of synthetic methods devised to construct these motifs. One of the most straightforward syntheses is through the oxidation of cyclic ethers/amines, readily available substrates already possessing the carbon backbone of the desired lactones and lactams. Benzylic heterocycles (e.g. Isocoumaran) can readily be oxidized to the corresponding products (e.g. Phtoalide). However, the oxidation of cyclic, non-benzylic ethers/amines remains a challenging task and a high-energy process, partly due to the relatively inert property of such α-C-Hs. Efforts have involved the use of metallic reagents/catalysts such as Ru,[2] Cr,[3] Cu,[4] Fe,[5] and Ir[6] in the non-benzylic cyclic ether/amine oxidation.[7] In contrast, sporadic studies have been reported on nonmetallic-based methods.[8]

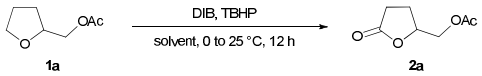
We have recently established a DIB/TBHP oxidation protocol which was applied to the allylic oxidation,[9a] the oxidation of unactivated and remote methylene $sp^3$ C-Hs to ketones,[9b] and the transformation of azides to aryl nitriles.[9c] In these studies, bis(*tert*-butylperoxy)iodobenzene, which was generated *in situ* by the reaction between diacetoxyiodobenzene (DIB) and *tert*-butyl hydroperoxide (TBHP), is believed to be the active species which can provide a reactive but controllable *t*BuOO• for the methylene proton abstraction.[10] We rationalized that the DIB/TBHP protocol can also activate the inert methylene C-H bonds adjacent to oxygen/nitrogen in cyclic ethers/amines, which can offer the corresponding lactone/lactam products.[11] Herein, we are pleased to disclose our recent development of a new synthetic method for the construction of non-benzylic lactones/lactams employing simple reaction setup and readily available reagents, and under mild conditions. In addition, unexpected ring-opeing/oxygen insertion products were obtained when alkyl and aryl α-substituents were used.




**Scheme 1** Summary of the oxidation reactions in this manuscript.

An initial experiment was performed using (tetrahydrofuran-2-yl)methyl acetate (**1a**) together with DIB/TBHP in $CH_2Cl_2$. After 12 h, the reaction was quenched with sodium sulfite to afford a 29% isolated yield of the desired product (5-oxotetrahydrofuran-2-yl)methyl acetate (**2a**) (Table 1, entry 1). Encouraged by this

**Table 1.** Optimization of the oxidation of **1a**.




**1a** **2a**

| Entry[a] | solvent | DIB (eqiv) | TBHP (eqiv) | Yield[b] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 2 | 4 | 29 |
| 2 | $CH_2Cl_2$ | 3 | 3 | 33 |
| 3 | $CH_2Cl_2$ | 4 | 3 | 31 |
| 4 | $CH_2Cl_2$ | 3 | 3 | 26 |
| 5 | $CH_2Cl_2$ | 3 | 3 | 28 |
| 6 | $CH_2Cl_2$ | 3 | 3 | 33 |
| 7 | MeCN | 3 | 3 | 21 |
| ***8*** | ***$MeNO_2$*** | ***3*** | ***4*** | ***65*** |
| 9 | $CHCl_3$ | 3 | 4 | 38 |
| 10 | $H_2O$ | 3 | 4 | 55 |
| 11 | toluene | 3 | 4 | 23 |
| 12 | 1:1 MeCN : $H_2O$ | 3 | 4 | 35 |
| 13 | EtOAc | 3 | 4 | 28 |
| 14 | *n*BuOAc | 3 | 4 | 39 |

[a] Reactions were carried out with **1a** (0.5 mmol) in solvent (1 mL) for 12 h. [b] Isolated yield.

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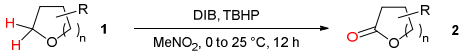
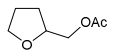
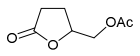
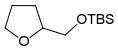
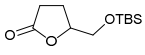
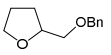
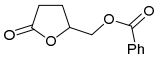
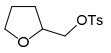
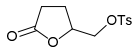
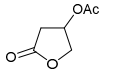
preliminary study, further optimizations were carried out. The ratio of DIB/TBHP was firstly varied and the reaction was found to give an isolated yield up to 33% when the ratio was 3:4 (Table 1, entries 2–6). Having identified the appropriate ratio of DIB and TBHP, various solvents were screened and nitromethane was found to afford 65% of the lactone product (Table 1, entries 7–14). It is noteworthy that the reaction proceeded smoothly even when using pure water as the solvent (Table 1, entry 10).

With the optimized conditions identified, some cyclic ether substrates were examined and the results are summarized in Table 2.[12] In general, the reaction selectivity of cyclic ethers proceeded smoothly to yield the corresponding lactones with good conversions. Moreover, excellent chemo- and regioselectivities were observed, wherein the reaction occurred on the less sterically-hindered side of the cyclic ether systems. We attempted to subject the lactone product **2a** under the optimized conditions. After 72 h, **2a** was recovered quantitatively and no over-oxidized product was detected. The oxidation protocol is also highly compatible with various protecting and functional groups including *tert*-butyldimethylsilyl (TBS), acetyl, benzoyl, and tosyl groups (Table 2, entries 1–5). In addition, other than five member ring system, six member ring system also returned with good reaction yield (Table 2, entry 7).

**Table 2.** Oxidation of Cyclic Ethers **1** to Lactones **2**.



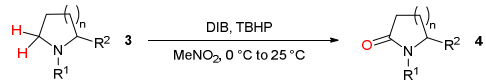

| entry[a] | substrate | | product | | yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  | **1a** |  | **2a** | 65 |
| 2 |  | **1b** |  | **2b** | 39(40) |
| 3[c] |  | **1c** |  | **2c** | 61 |
| 4 |  | **1d** |  | **2d** | 42(42) |
| 5 |  | **1e** |  | **2e** | 34(20) |
| 6 |  | **1f** |  | **2f** | 50 |
| 7 |  | **1g** |  | **2g** | 68 |

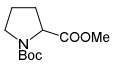
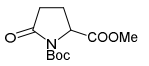
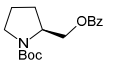
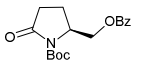
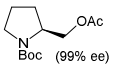
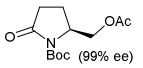
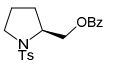
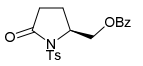
[a] Reactions were carried out with **1** (0.5 mmol), DIB (1.5 mmol), TBHP (2.0 mmol), in $MeNO_2$ (1.0 mL) for 12 h. [b] Isolated yield. The amount of unreacted starting material **1** was determined by $^1$H NMR and indicated in the parentheses. [c] DIB (3.0 mmol) and TBHP (4.0 mmol) were used.

Other than the oxidation of cyclic ethers, we have also examined the oxidation of cyclic amines to lactams (Table 3). Under the optimized conditions, *N*-Boc and *N*-Ac pyrrolidines **3a** and **3b** returned with good conversions. In fact, we have also examined *N*-methyl pyrrolidine and no desired lactam was detected.[13] It appears that the electronic demand at the nitrogen plays a crucial role in the reactivity; an electron-rich pyrrolidine gave a direct *N*-oxidation product, while a relatively electron-deficient system suffered from lower reactivity. Similar to the cyclic ether oxidation, the oxidation of cyclic amines (5- and 6-membered rings) returned with good conversions and functional groups compatibility. More importantly, the L-proline-derived substrate **3e** gave the desired product **4e** with retention of enantiomeric purity, which suggests that the C-H abstraction did not take place at the more substituted carbon.[14]

Towards the understanding of mechanism, a plausible pathway is proposed and illustrated in Scheme 1. The *tert*-butylperoxy radical may abstract the α-heteroatom proton of **A** to generate the α-heteroatom radical **B**, potentially stabilized by the heteroatom. Coupling of *t*BuOO• with species **B** can produce the peroxy ether intermediate **C**, which was evidenced by the successful isolation

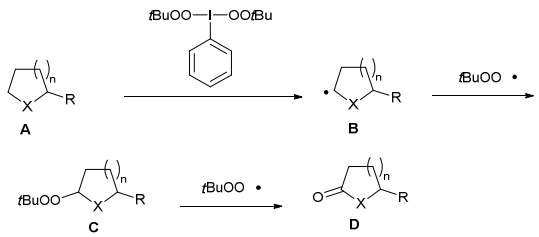
**Table 3.** Oxidation of Cyclic Amines **3** to Lactams **4**.




| entry[a] | substrate | | product | | time (h), yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  | **3a** |  | **4a** | 18, 63 |
| 2 |  | **3b** |  | **4b** | 18, 51(38) |
| 3 |  | **3c** |  | **4c** | 18, 40(32) |
| 4 |  | **3d** |  | **4d** | 12, 71 |
| 5 |  | **3e** |  | **4e** | 12,47(32) |
| 6 |  | **3f** |  | **4f** | 12, 23(69) |
| 7 |  | **3g** |  | **4g** | 18, 52(37) |
| 8 |  | **3h** |  | **4h** | 18, 48(34) |

[a] Reactions were carried out with **3** (0.5 mmol), DBH (0.12 mmol) in solvent (5 mL) at –60 ºC. [b] The reaction was conducted at –50 ºC. [c] Isolated yield.

of species C (X = O, R = H).[15] Subsequent oxidation of C can provide the desired lactone or lactam product D. Moreover, the reaction was terminated immediately upon the addition of butylated hydroxytoluene (BHT), which indicated the radical nature of the reaction.




**Scheme 1** Proposed Mechsnism of the oxidation reaction resulting in the formation of lactones and lactams.

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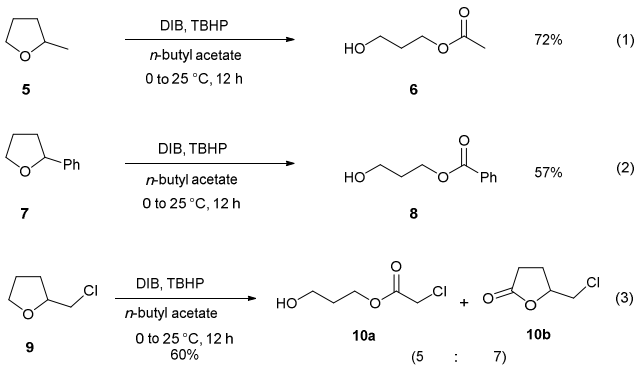
We attempted to further explore the substrate scope. Surprisingly, when 2-methyltetrahydrofuran (5) and 2-phenyltetrahydrofuran (7) were oxidized using the DIB/TBHP protocol, no lactone was detected. Instead, unusual ring-opening hydroxyl-esters 6 and 8 were isolated as the sole products, respectively (Scheme 2, eq 1 and 2). When the chlorinated ether was used as the substrate, a mixture of ring-opening product and lactone (5:7, ratio determined by $^1$H NMR) was detected (Scheme 2, eq 3). Although the mechanistic pathway that leads to such ring-opening products remains unclear, these results suggest that the electronic properties of the substituents can affect the oxidation's positional selectivity.[16]




**Scheme 2** Examination on Other Substrates.

In summary, we have developed a novel C-H oxidation of cyclic ethers and amines to the corresponding lactones and lactams using a DIB/TBHP protocol. The reaction is mild and no metallic reagent is involved. Further investigation on the mechanism is underway.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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12 Representative procedure for the oxidation**:** To a solution of (tetrahydrofuran-2-yl)methyl acetate (**1a**) (72 mg, 0.50 mmol) in nitromethane (1 mL) was added diacetoxyiodobenzene (484 mg, 1.5 mmol) at 0 °C. The resultant suspension was vigorously stirred and a solution of *tert*-butylhydroperoxide (5.0 M in decane, 400 µL, 2.0 mmol) was added dropwise over 30 min. After 12 hours, the reaction was quenched with $Na_2SO_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography eluted with *n*-hexanes/EtOAc (2:1) to yield (5-oxotetrahydrofuran-2-yl)methyl acetate (**2a**) as a yellow oil (51 mg, 65%).

13 A very polar product was detected in the reaction which is believed to be the *N*-oxide compound.

14 J. Sperry, *Synthesis*, 2011, 3569–3580 and references cited therein.

15 It was evidenced by the successful isolation of peroxy ether **C** (X = O, R = H, n = 1) when the reaction of THF with DIB/TBHP was quenched at 0 °C. Subjecting the intermediate **C** (X = O, R = H, n = 1) under standard oxidation condition gave the desired lactone **D** (X = O, R = H, n = 1).

16 We speculate that the key step involves the proton abstraction of **5** (or **7**) may occur at the tertiary carbon to yield the corresponding tertiary radical species, followed by the coupling of *tert*-butylperoxy radical. However, this remains unclear and is subjected to further investigation.