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Multifunctionalization of alkenes *via* aerobic oxynitration and sp^3 C–H oxidation†

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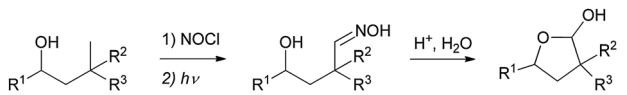
A method for direct functionalization of three positions including an unactivated C–H bond of aliphatic alkenes using *tert*-butyl nitrite and molecular oxygen to give γ-lactols has been developed. The present reaction proceeds through a sequence of radical processes involving oxynitration followed by aerobic oxidation of an sp^3 C–H bond. This multifunctionalization reaction requires neither metallic reagents nor photolysis and proceeds under mild conditions.

Direct functionalization reactions of an unactivated sp^3 C–H bond have large potential for changing existing methodologies in synthetic chemistry.[1,2] Transition metal-catalyzed methods have recently become the mainstream of C–H activation chemistry,[3] but C–H functionalization reactions without transition metal reagents would be more efficient methods from economical and environmental viewpoints.[4] Among the various approaches to transition metal-free sp^3 C–H functionalization, methods using radical species have been developed over the past century.[5] In 1960, Barton and co-workers reported introduction of an oxime group into an unactivated methyl group using a photolysis reaction of a nitrite compound in studies on steroid chemistry (Scheme 1).[6] Photolysis of the nitrite compound generates the corresponding highly reactive alkoxy radical, and it transformed a methyl group into an oxime group *via* 1,5-hydrogen shift followed by trapping of the resultant radical by nitrogen oxide.[7] Although this "Barton reaction" has often suffered from low yield of the product, it has been established as a valuable synthetic method for a direct functionalization on an unactivated alkyl group through the application to synthesis of biologically active compounds.[8] Thus, radical methodologies continue to contribute to the development of C–H functionalization chemistry from a different angle from other methods.[9]

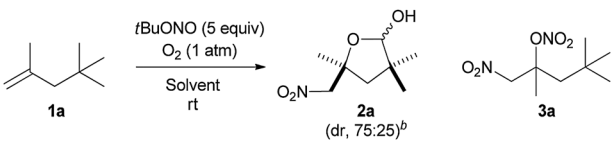


Scheme 1 The Barton reaction.

Recently, we have reported a radical oxynitration reaction of alkenes using *tert*-butyl nitrite and molecular oxygen.[10] In the course of this study, we found that γ-lactols were directly produced from simple aliphatic alkenes by oxynitration of an olefin and aerobic oxidation of an sp^3 C–H bond in which 1,5-hydrogen shift of an intermediary alkoxy radical was thought to be involved.[11,12] Herein, we report a unique multifunctionalization reaction of alkenes using non-metallic reagents under mild conditions.

Treatment of alkene **1a**, which was chosen as a model substrate to optimize conditions, with 5 equivalents of *tert*-butyl nitrite (*t*BuONO) in pentane under an oxygen (O_2) atmosphere at room temperature gave γ-lactol **2a** in 11% yield along with a small amount of nitrate ester **3a** (Table 1, entry 1). Although the reaction in dichloromethane (CH_2Cl_2) slightly improved the yield of γ-lactol **2a** (entry 2), we realized from the results that the reaction in a nonpolar

Table 1 The effect of solvent in oxidative nitration of alkene **1a**[a]



1a → **2a** (dr, 75:25)[b] + **3a**

Entry	Solvent	Time (h)	Yield[c] (%) 2a	3a
1	Pentane	5	11	5
2	CH_2Cl_2	5	20	8
3	MeOH	8	—	—
4	THF	5	15	44
5	DMF	5	36	36
6	DMSO	5	52	21
7[d]	DMSO	5	44	21
8[e]	DMSO	12	26	24

[a] Reaction conditions: **1a** (0.6 mmol), *t*BuONO (3.0 mmol) in solvent (3 mL) under an O_2 atmosphere (1 atm). [b] Diastereomeric ratio was approximately estimated by ^{1}H NMR analysis. [c] Isolated yield. [d] 3 equiv. of *t*BuONO (1.8 mmol) was employed. [e] Under air (1 atm).

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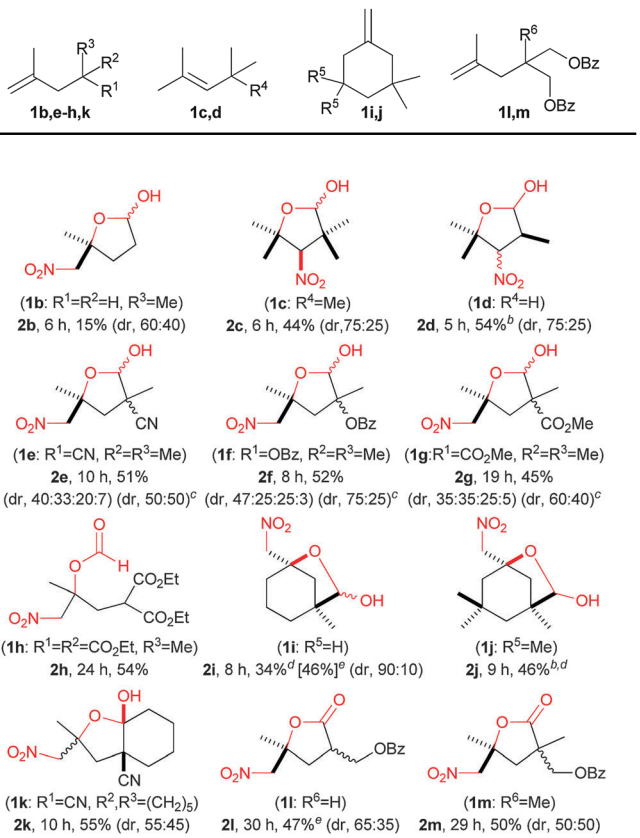
solvent was sluggish. The use of methanol (MeOH) as a solvent caused decomposition of the starting material or products, and no identifiable product was obtained (entry 3). In the reaction in tetrahydrofuran (THF), the total yield of products **2a** and **3a** was improved, but undesired **3a** was the major product (entry 4). When the reaction was carried out in *N*,*N*-dimethylformamide (DMF), equal amounts of **2a** and **3a** were obtained in good total yield (entry 5). Results of entries 4 and 5 clearly indicated that polarity of the aprotic solvent significantly affects the ratio of **2a** and **3a**. Therefore, we examined the use of dimethylsulfoxide (DMSO), which is an excellent polar aprotic solvent, and found that γ-lactol **2a** was obtained as the major product (entry 6). A decrease in the amount of *t*BuONO or the use of air did not improve the results (entries 7 and 8).

Subsequently, transformation of several alkenes into γ-lactols was examined (Table 2). The branched structure of substrates was likely to be important in the reaction because a dramatic difference in yields of products **2a** and **2b** was observed between branched **1a** and linear **1b**. This clearly indicates that an intramolecular process is involved in the C–H oxidation. Internal alkenes **1c** and **1d** also gave γ-lactols **2c** and **2d** in reasonable yields. When alkenes **1e–g** having functional groups such as nitrile, benzoyloxy or ester were employed as substrates, γ-lactols **2e–g** were obtained in similar yields, though these are mixtures of four diastereoisomers. On the other hand, C–H oxidation on a methyl group of malonate derivative **1h** seemed to proceed, but a subsequent C–C bond cleavage occurred to give formate ester **2h**. Reactions of methylenecyclohexane derivatives **1i** and **1j** provided bicyclic compounds **2i** and **2j** in acceptable yields along with a small amount of the corresponding ring-opening aldehydes. Like these entries, γ-lactol products obtained by this reaction were not necessarily stable, and partial degradation of products in the course of the reaction or purification was presumed in several cases. For instance, the yield of **2i** estimated by ^{1}H NMR analysis of the crude product was higher than the isolated yield. We also found that this reaction caused C–H oxidation at a methylene position of alkene **1k** to give bicyclic compound **2k**. In the reaction of alkenes **1l** and **1m**, C–H oxidation on a benzoyloxymethyl group predominantly proceeded to provide γ-lactone derivatives **2l** and **2m**.

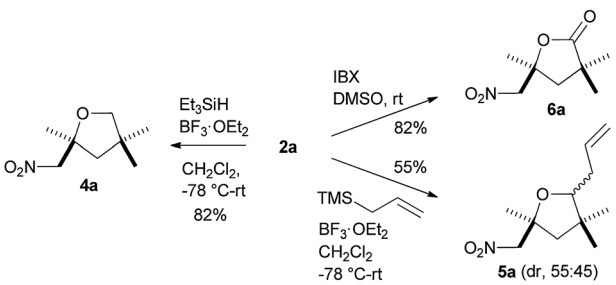
Table 2 Multifunctionalization reactions of various alkenes[a]



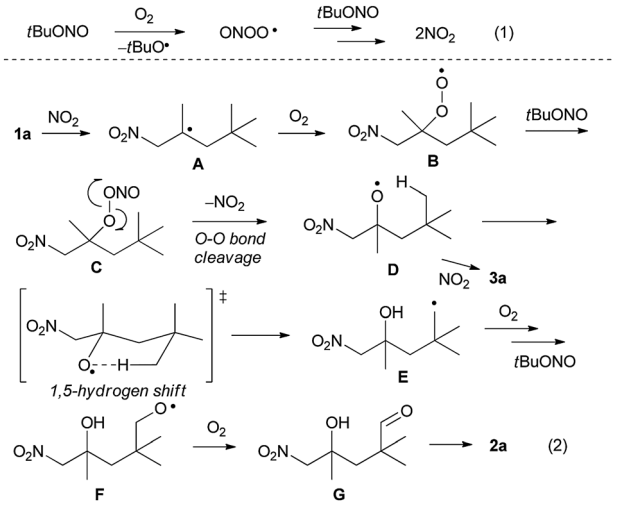
[a] Reaction conditions: **1b–m** (0.6 mmol), *t*BuONO (3.0 mmol) in DMSO (3 mL) under an O_2 atmosphere (1 atm) at room temperature. Isolated yield. Diastereomeric ratios (dr) were approximately estimated by ^{1}H NMR analysis. [b] Single stereoisomers at the hemiacetal carbon (unassigned) were detected by ^{1}H NMR analysis. [c] Diastereomeric ratios of the corresponding lactones (approximately estimated by ^{1}H NMR analysis after oxidation of **2e–g** with Dess–Martin periodinane, see the ESI). [d] Isolated along with a small amount of the corresponding ring-opening aldehyde (**2i** : 92 : 8, **2j** : 93 : 7, estimated by ^{1}H NMR analysis). [e] Yield determined by ^{1}H NMR analysis using an internal standard (mesitylene).

The obtained γ-lactol **2a** can be transformed into several oxygen-containing heterocyclic systems (Scheme 2). Reduction of γ-lactol **2a** with triethylsilane (Et_3SiH, 2 equiv.) in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$, 2 equiv.) afforded tetrahydrofuran derivative **4a**.[13] The use of allyltrimethylsilane ($TMSCH_2CH{=}CH_2$, 2 equiv.) instead of triethylsilane resulted in formation of a new C–C bond to afford substituted tetrahydrofuran derivative **5a**. In addition, γ-lactol **2a** was easily oxidized to γ-lactone derivative **6a** with iodoxybenzoic acid (IBX, 5 equiv.).[14] Thus, it is noteworthy that the *tert*-butyl nitrite-mediated reaction allows us to gain functionalized compounds bearing higher oxidation levels from simple unsaturated hydrocarbons in only one or two steps.

A proposed mechanism of this multifunctionalization involving sp^3 C–H oxidation is shown in Scheme 3. Although the exact pathway is unclear, it is likely that nitrogen dioxide (NO_2) is generated from *t*BuONO by oxidation with molecular oxygen.[10,15] The peroxynitrite radical formed by aerobic cleavage of the weak N–O bond of *t*BuONO might be a strong candidate as an intermediate to provide NO_2 (Scheme 3, eqn (1)).[7,16] Addition of NO_2 to alkene **1a** would generate tertiary alkyl radical **A** followed by trapping by molecular oxygen to give peroxy radical **B**.[17] It is reasonable that radical **B** reacts with *t*BuONO to afford peroxynitrite **C** because *t*BuONO can work as a nitrogen oxide source.[10] As the key step of C–H oxidation, highly reactive alkoxy radical **D** formed by the O–O bond cleavage of intermediate **C** gives rise to a 1,5-hydrogen



Scheme 2 Derivatives from γ-lactol **2a**.



Scheme 3 A proposed mechanism.

shift of a methyl group to generate alkyl radical **E**.[7,18] The reaction of radical **E** with molecular oxygen and *t*BuONO would afford alkoxy radical **F** through a similar pathway.[18] Oxidation of alkoxy radical **F** by oxygen would produce the corresponding aldehyde **G** followed by rapid intramolecular hemiacetalization to give **2a** (Scheme 3, eqn (2)).[19]

In conclusion, we found a novel multifunctionalization reaction involving direct sp^3 C–H oxidation of aliphatic alkenes using *tert*-butyl nitrite and molecular oxygen. This reaction would consist of a sequence of radical processes including oxynitration of the olefin and C–H oxidation *via* a 1,5-hydrogen shift. Although there might still be room for improvement in the yield of products, one-step transformation of aliphatic alkenes into γ-lactols with introduction of a nitrogen atom is unprecedented. In addition, the reaction can be conducted under mild conditions using inexpensive reagents including no metallic compound, and the use of molecular oxygen as an oxygen source is ideal.[20] Our work has demonstrated that transformation of simple organic molecules into highly functionalized compounds can be achieved even with a simple and common reaction system. We believe that such ''simple and advanced reactions'' are promising in the development of useful synthetic methods involving direct C–H functionalization.

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