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Oxidative Nitration of Alkenes with *tert*-Butyl Nitrite and Oxygen

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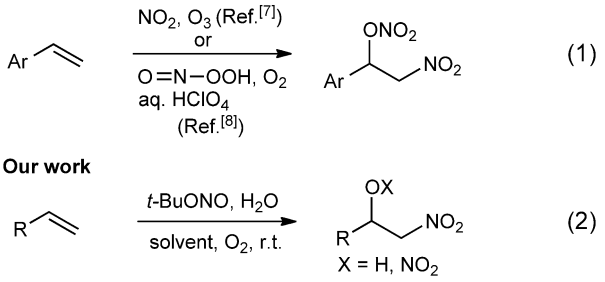
Abstract: A method for the oxidative nitration of alkenes using a combination of *tert*-butyl nitrite and molecular oxygen to give β-nitro alcohols and their nitrate derivatives has been developed. The present reaction provides a practical method for the synthesis of nitro compounds because of the mild reaction conditions, the use of inexpensive reagents and a simple experimental procedure.

Keywords: alkenes; nitration; nitrites; oxygenation; radical reactions

Nitro compounds are useful for medicines, industrial materials and fuels.[1] Such compounds are also valuable synthetic intermediates in organic chemistry. For example, reduction and Nef reaction of nitro compounds afford the corresponding amines and ketones.[2] Nitro-aldol reactions and nitro-Michael reactions have been extensively used for C–C and C–X (X = N, O) bond formation.[3] Many nitration methods for the synthesis of aromatic and aliphatic nitro compounds have been developed.[4,5] A method for the nitration of alkenes is an important tool for the synthesis of nitroalkenes and nitroalkanes. Nitrogen dioxide gas (NO_2), which is a free radical, is one of the simplest and most common nitration reagents.[6] Suzuki and Mori reported the oxidative nitration of styrene derivatives using a combination of NO_2 and ozone (O_3).[7] Grossi and co-workers reported the radical nitration of styrene using peroxynitrite to give 2-nitro-1-phenylethyl nitrite along with some by-products [Scheme 1, Eq. (1)].[8,9] NO_2 is an economic nitrogen source in industrial chemistry, but its extreme reactivity and toxicity restrict its application to reactions. Also, the complication of handling NO_2 gas has limited its use by chemists in the laboratory. Herein, we report a practical oxidative radical nitration of alkenes using commercially available *tert*-butyl nitrite (*t*-BuONO) and molecular oxygen [Scheme 1, Eq. (2)].[10]

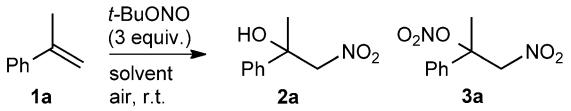


Scheme 1. Oxidative radical nitrations of alkenes.

Treatment of α-methylstyrene (**1a**) with *t*-BuONO (3 equiv.) in toluene under air gave β-nitro alcohol compound **2a** in moderate yield along with its nitrate derivative **3a** (Table 1, entry 1). The reaction in MeOH gave an improvement in the result to some extent (entry 2). When water was used as a solvent, disappearance of the starting material in shortened reaction time was observed (entry 3). Encouraged by this result, addition of an amount of water solvent to the reaction mixture in toluene (toluene-H_2O, 1:1) was tested for improved total yield of products **2a** and **3a** (entry 4). After screening several solvents (entries 5–8), we found that the use of hexane as a solvent gave the β-nitro alcohol compound **2a** in good yield in a short reaction time (entry 8). A decrease in the amount of water (3 equiv.) added to the reaction mixture in hexane was ineffective (entry 9). An unchanged result was obtained under diluted conditions (entry 10). When isoamyl nitrite (*i*-AmONO) or pure oxygen gas was used, the yield of the product was not improved (entries 11 and 12).

Next, reactions of several styrene-type alkenes were examined (Table 2). Our preliminary experi-

Table 1. Optimizations of nitration reaction of α-methylstyrene.[a]



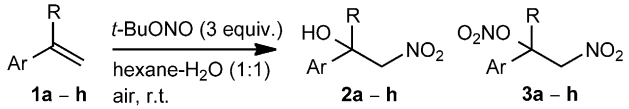
Entry	Solvent	Time [h]	Yield [%][b] 2a	3a	Conversion [%][c]
1	toluene	120	32	20	93
2	MeOH	48	51	9[d]	>99
3	H_2O	2.5	45	–	>99
4	toluene-H_2O (1:1)	3	48	28	94
5	THF-H_2O (1:1)	3	60	–	95
6	CH_2Cl_2-H_2O (1:1)	2	40	31	95
7	EtOAc-H_2O (1:1)	2	41	19	93
8	hexane-H_2O (1:1)	3	74	–	>99
9[e]	hexane	6	26	32	96
10[f]	hexane-H_2O (1:1)	3	71	–	>99
11[g]	hexane-H_2O (1:1)	17	56	–	>99
12[h]	hexane-H_2O (1:1)	1.5	54	–	97

[a] *Reaction conditions:* **1a** (0.4 mmol), *t*-BuONO (1.2 mmol) and in solvent (2.5 mL) under air (1 atm).
[b] Isolated yield.
[c] Conversion was determined by GC analysis with dodecane as an internal standard.
[d] 2-Methoxy-1-nitro-2-phenylpropane was obtained instead of **3a**.
[e] 3 equivalents of water (21.6 μL) were added.
[f] A solution of *t*-BuONO (1.2 mmol) in hexane (2.5 mL) was added to a solution of **1a** (0.4 mmol) in hexane (2.5 mL)-H_2O (5 mL) over 1 h and the mixture was further stirred for 2 h.
[g] *i*-AmONO was employed instead of *t*-BuONO.
[h] Under O_2 atmosphere (1 atm).

ments showed that diluted conditions (Table 1, entry 10) gave better results than normal conditions (Table 1, entry 8) in many of reactions using styrene-type alkenes except **1a**.[11] Reactions of α-methylstyrene derivatives bearing *p*-methoxyphenyl, *p*-nitrophenyl, *p*-halophenyl and β-naphthyl groups gave β-nitro alcohol compounds **2b–f** as major products (Table 2, entries 2–6). In the case of styrene (**1g**), β-nitro alcohol compound **2g** and its nitrate derivative **3g** were obtained in moderate yields, respectively (entry 7). Nitration of 1,1-diphenylethene (**1h**) gave β-nitro alcohol compound **2h** in moderate yield (entry 8). In the most of cases, small amounts of aromatic ketone derivatives (e.g., acetophenone) as decomposition by-products were observed,[8] whereas no regioisomer (2-nitro-1-hydroxy or nitroxy product) was detected.[7]

The reaction of ethyl methacrylate (**4a**) under conditions similar to those in reactions of styrene derivatives (Table 1, entry 10) was not completed and unsat-

Table 2. Nitration of various styrene-type alkenes.[a]



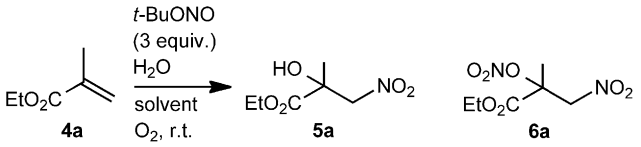
Entry	1		Time [h][b]	Yield [%][c] 2	3	Conversion [%][d]
						
1	Ar = C_6H_5	**a**	3	71	-	>99
2	Ar = 4-$MeOC_6H_4$	**b**	1	60	-	>99
3	Ar = 4-$NO_2C_6H_4$	**c**	6	41	27	>99
4	Ar = 4-FC_6H_4	**d**	1.5	62	-	>99
5	Ar = 4-BrC_6H_4	**e**	2	59	10	>99
6	Ar = β-$C_{10}H_7$	**f**	1	64	9	98
7		**g**	3	34	20	98
8		**h**	1	38	-	97

[a] *Reaction conditions:* **1a–h** (0.4 mmol), *t*-BuONO (1.2 mmol) in hexane (5 mL)-H_2O (5 mL) under air (1 atm) (conditions of Table 1, entry 10).
[b] Including the addition time (1 h) of a *t*-BuONO solution in hexane.
[c] Isolated yield.
[d] Conversion was determined by GC analysis with dodecane as an internal standard.

isfactory results for the yields of products **5a** and **6a** were obtained (Table 3, entry 1). Therefore, we tried to optimize the conditions of the reaction using alkene **4a**. The use of pure oxygen gas instead of air gave a slightly improved result (entry 2). A decrease in the amount of water added to the reaction mixture gave an improved yield of products in this case (entry 3). After examination of some solvents (entries 4–6), we found that the use of CH_2Cl_2 as a solvent almost exclusively gave nitrate product **6a** in good yield in a short reaction time (entry 6) and diluted conditions were unnecessary in this reaction (entry 7).

Finally, the oxidative nitrations of various alkenes were investigated (Table 4). Like the reaction of styrene-type alkenes, yields of isolated products were inferior to conversion ratios of starting materials due to the generation of decomposition by-products, but no regioisomer was observed at all. Reactions of other α,β-unsaturated esters **4b** and **4c** similarly afforded nitrate products **6b** and **6c**, respectively (Table 4, entries 2 and 3). When aliphatic alkene **4d** was employed as a substrate, a low yield (26%) of nitrate derivative **6d** was obtained under conditions using an excessive amount of water in hexane (hexane-H_2O, 1:1 under air), whereas treatment of alkene **4d** with *t*-BuONO in the presence of 3 equivalents of water in CH_2Cl_2 gave compound **6d** in 75% yield (entry 4). Reactions of several aliphatic alkenes **4e–h** also led to

Table 3. Optimizations of nitration reaction of ethyl methacrylate.[a]



Entry	Solvent	H_2O (equiv.)	Time [h]	Yield [%][b] 5a	6a	Conversion [%][c]
1[d,e]	hexane	excess	46	20	22	83
2[d]	hexane	excess	46	27	21	88
3	hexane	3	7	39	26	>99
4	toluene	3	7	29	38	>99
5	THF	3	10	34	35	>99
6	CH_2Cl_2	3	4	8	52	>99
7[f]	CH_2Cl_2	3	2	2	66	>99

[a] *Reaction conditions:* **4a** (0.4 mmol), *t*-BuONO (1.2 mmol) in solvent (10 mL) under O_2 atmosphere (1 atm).
[b] Isolated yield.
[c] Conversion was determined by GC analysis with dodecane as an internal standard.
[d] A solution of *t*-BuONO (1.2 mmol) in hexane (2.5 mL) was added to a solution of **4a** (0.4 mmol) in hexane (2.5 mL)-water (5 mL) over 1 h and the mixture was further stirred for 45 h.
[e] Under air (1 atm).
[f] The reaction was performed in 2 mL of CH_2Cl_2.

the corresponding nitro compounds **5e–h** and **6e–h** in good total yields (entries 5–8). This reaction enabled an access to cyclic nitro compounds **5i**, **j** and **6i**, **j** from cycloalkenes **4i** and **4j**, respectively (entries 9 and 10). When 1,6-diene **4k** was employed as a substrate, five-membered ring compounds **5k** and **6k** were obtained (entry 11). Compounds **5k** and **6k** were certainly produced *via* 5-*exo*-*trig* cyclization of a radical generated by addition of NO_2 to one olefin, therefore, this result supports the radical mechanism in the present nitration reaction.[12]

A plausible mechanism of this oxidative nitration is shown in Scheme 2. Water would cause a gradual hydrolysis of *t*-BuONO to generate nitrous acid (HNO_2) [Scheme 2, Eq. (1)].[13] It is known that HNO_2 is an unstable compound and that its decomposition gives NO_2 and nitrogen monoxide (NO) [Scheme 2, Eq. (2)].[14,15] NO is rapidly oxidized into NO_2 in the presence of oxygen [Scheme 2, Eq. (3)].[16] Addition of NO_2 to alkene would give radical intermediate **A**. Trapping of radical **A** by molecular oxygen leads to the formation of peroxy radical intermediate **B** followed by reaction with *t*-BuONO to give peroxynitrite **C**. The cleavage of the O–O bond of peroxynitrite **C** would easily takes place to generate alkoxy radical intermediate **D**, and radical coupling of **D** with NO_2 gives nitrate product.[8] It is presumed that a β-nitro alcohol compound is mainly produced by hydrolysis of a nitrate compound. The dominant production of β-nitro alcohol compounds **2a–h** from styrene derivatives **1a–h** can be explained by an S_N1 hydrolysis and/or simple ester hydrolysis of a nitrate ester compound in the presence of excessive water. Simple ester hydrolysis of nitrate esters is unlikely to be a fast process because the reaction of α,β-unsaturated ester **4a** gave nitrate compound **6a**, which would not be hydrolyzed *via* an S_N1 mechanism, in a reasonable yield along with β-nitro alcohol compound **5a** even under conditions in the presence of excessive water (Table 3, entries 1 and 2). Additionally, since the reaction in the absence of water proceeded slowly (Table 1, entry 1), another mechanism for the generation of NO_2 must be considered as well. A homolytic cleavage of the N–O bond of *t*-BuONO might take place slowly to give *tert*-butoxy radical and NO followed by generation of NO_2 in the presence of oxygen [Scheme 2, Eqs. (3) and (4)].[17] Perhaps, *t*-BuONO might be directly oxidized by molecular oxygen to generate NO_2 *via* peroxynitrite radical ($ONOO^{\bullet}$)[16c] [Scheme 2, Eq. (5)]. The production of β-nitro alcohol compounds could be explained by a direct hydrogen abstraction by alkoxy radical intermediate **D** from the solvent.

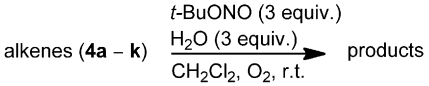
In conclusion, we have developed an efficient oxidative nitration of alkenes. The addition of water has been demonstrated to be important for obtaining a good result in the present reaction. This reaction has the following advantages: (i) all reagents herein employed are easily available and inexpensive and (ii) reaction conditions are mild and the experimental procedure is very simple and safe. Therefore, the present reaction will provide a general and practical method for the synthesis of β-oxygenated nitro compounds.

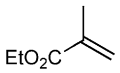
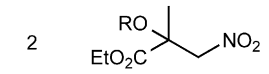
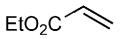
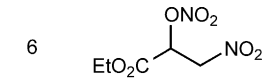
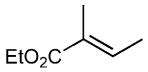
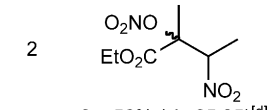
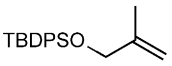
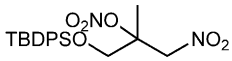
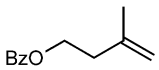
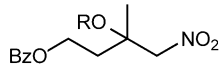
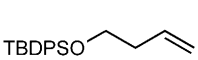
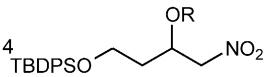
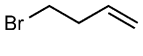
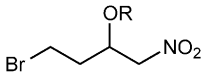
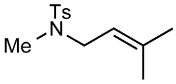
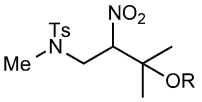
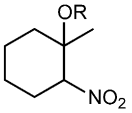
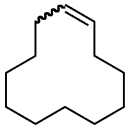
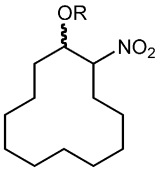
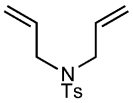
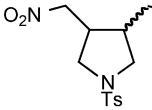
Experimental Section

General Procedure of Reactions using Styrene-Type Materials

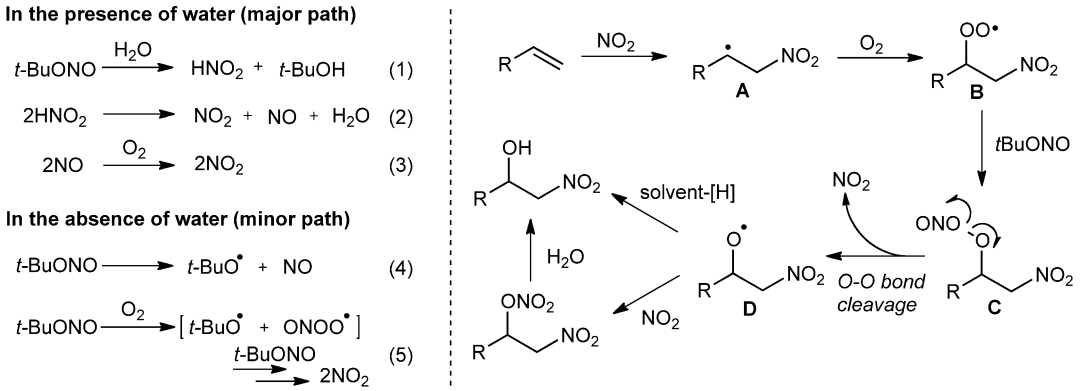
To a solution of alkene (0.4 mmol) in hexane (2.5 mL) and water (5 mL) was added a solution of *t*-BuONO (123.7 mg, 1.2 mmol) in hexane (2.5 mL) over 1 h under air (1 atm), and the mixture was further stirred at room temperature until disappearance of the starting material. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine and dried with $MgSO_4$ and filtered. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-EtOAc) to give nitrated products.

Table 4. Nitration of various alkenes.[a]



Entry	4		Time [h]	Products/Yield[b]	Conv.[c]
1		**a**	2	 **5a** (R = H): 2% **6a** (R = NO_2): 66%	>99%
2		**b**	6	 **6b**: 30%	>99%
3		**c**	2	 **6c**: 56% (*dr*, 65:35)[d]	>99%
4		**d**	3	 **6d**: 75% (26%)[e]	92%
5		**e**	2	 **5e** (R = H): 25% **6e** (R = NO_2): 62%	>99%
6		**f**	4	 **5f** (R = H): 16% **6f** (R = NO_2): 57%	93%
7		**g**	4	 **5g** (R = H): 18% **6g** (R = NO_2): 41%	>99%
8		**h**	9	 **5h** (R = H): 11% **6h** (R = NO_2): 57%	98%
9		**i**	2	 **5i** (R = H): 19% (*dr*, >95:5)[d] **6i** (R = NO_2): 36%	>99%
10	 (mixture of *cis* and *trans*)	**j**	1.5	 **5j** (R = H): 16% (*dr*, 65:35)[d] **6j** (R = NO_2): 52%	97%
11		**k**	48	 **5k** (R = H): 12% (*dr*, 70:30)[d] **6k**(R = NO_2): 56% (*dr*, 80:20)[d]	>99%

[a] *Reaction conditions:* **4a–k** (0.4 mmol), *t*-BuONO (1.2 mmol) and H_2O (1.2 mmol) in CH_2Cl_2 (2 mL) under O_2 atmosphere (1 atm).
[b] Isolated yield.
[c] Conversion was determined by GC analysis with dodecane as an internal standard.
[d] Diastereomeric ratio was estimated by ^1H NMR analysis.
[e] The reaction was carried out under conditions of Table 1, entry 10 [in hexane-H_2O (1:1), under air, 24 h].



Scheme 2. Plausible mechanism of radical nitration.

General Procedure of Reactions using α,β-Unsaturated Esters or Aliphatic Alkenes

To a solution of alkene (0.4 mmol) in CH_2Cl_2 (2 mL) was added water (21.6 μL, 1.2 mmol) and *t*-BuONO (123.7 mg, 1.2 mmol) under O_2 atmosphere (1 atm), and the mixture was further stirred at room temperature until disappearance of the starting material. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with $MgSO_4$ and filtered. After removal of solvent, the residue was purified by silica gel chromatography (hexane-EtOAc) to give the nitrated products.

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