Tetrahedron Letters 53 (2012) 1401–1405

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regio- and stereoselective hydroxybromination and dibromination of olefins using ammonium bromide and oxone®

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ARTICLE INFO

Article history:
Received 18 October 2011
Revised 4 January 2012
Accepted 6 January 2012
Available online 12 January 2012

Keywords:
Alkenes
Hydroxybromination
Dibromination
Regioselectivity
Stereoselectivity

ABSTRACT

An efficient protocol for the synthesis of vicinal bromohydrins and dibromides from olefins is presented. Various olefins are regio- and stereoselectively hydroxybrominated and dibrominated with *anti* fashion, following Markonikov's rule, using eco-friendly, non-toxic, and stable reagents such as NH_4Br and oxone® in CH_3CN/H_2O (1:1) and CH_3CN without employing catalyst in moderate to excellent yields. Bromohydrins are formed instantaneously.

Regioselective functionalization of olefins is an important process in synthetic organic chemistry. In particular, selective introduction of two functional groups, such as hydroxybromo and dibromo in a highly regio- and stereoselective manner remains an important and challenging task.[1] The resulting products (vicinal bromohydrins and dibromides) are versatile intermediates for the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals, additives, plasticizers, and specialty chemicals.[2]

Bromohydrins are usually prepared by the ring opening of epoxides[3] using hydrogen bromide or metal bromides. These procedures are generally associated with the formation of byproducts such as vicinal dibromides, 1,2-diols and these methods also require prior synthesis of epoxides. Apart from this, there are two general approaches for heterolytic addition of water and bromine to an olefinic bond. One, involves the use of molecular bromine or *N*-bromoimides[4,7] and the other uses metal bromide or HBr along with an oxidizing agent.[5,6]

Classical bromination involves the use of hazardous elemental bromine, which is a pollutant and generates hazardous HBr as byproduct. The use of *N*-bromoimide is a better alternative for molecular bromine, which does not produce HBr in the bromination of olefins, but they are expensive and generate organic waste. Other drawbacks of these methods are low yield and long reaction time.

At present, oxidative bromination continues to be of great interest because it precludes the use of volatile, hazardous bromine. A number of protocols are available to achieve bromination of alkenes using Br^- instead of Br_2. The oxidative bromination requires a metal salt as bromine source, an oxidizing agent and a catalyst to carry out the transformation. However, such oxidative brominations involve the use of heavier metals in stoichiometric amounts and often resulting in poor yields and selectivity (poor stereoselectivity and unwanted side products). Most of the reported methods for such transformation rely on modification of molecular bromine, *N*-bromoimides, or metal salts with an oxidizing agent, while the use of other reagents has been less investigated.[8,9] In spite of the variety of methods available for the preparation of *vic*-bromohydrins and dibromides directly from olefins, many of them often involve the use of expensive reagents and the formation of mixture of products resulting in low yields of the desired products. The replacement of such reagents by non-toxic, mild, selective, and easy-to-handle reagents is very desirable and represents an important goal in the context of clean synthesis.

Oxone®, a potassium triple salt containing potassium peroxy monosulfate, is an effective oxidant. Due to its stability, water-solubility, ease of transport, non-toxic 'green' nature, non-polluting byproducts, and cost-effectiveness, this solid reagent has become an increasingly popular reagent for oxidative transformations.[10–14] Oxone® is a commonly used reagent (oxidant) for the conversion of alkenes into epoxides.[15]

In continuation of our interest on the halogenation reactions, herein, we report a very simple, mild, and efficient method for the direct synthesis of bromohydrins and dibromides from olefins using NH_4Br as a bromine source and oxone® as an oxidant without catalyst in a highly regio- and stereoselective fashion in short

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doi:10.1016/j.tetlet.2012.01.026

reaction time (Scheme 1).[16,17] Bromination of olefins using NH_4Br and oxone® has not been studied so far.

Initially, we investigated the bromohydroxylation of styrene with NH_4Br and oxone® as the oxidant in various solvents such as CH_3CN, DCM, CCl_4, acetone, and in combination with water (Table 1, entries 1–17). The results obtained suggested that a mixture of acetonitrile and water in 1:1 ratio was the best solvent system for bromohydrin formation (Table 1, entry 10).

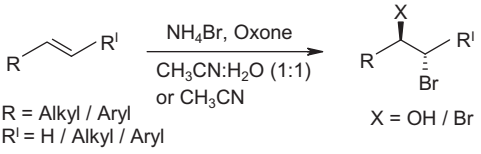
Stimulated by these affirmative preliminary results, we decided to examine the NH_4Br-oxone® reagent system for hydroxybromination on a number of different activated, inactivated, and moderately activated aromatic alkenes (Table 2, entries 2–7), asymmetric *trans*-alkenes (Table 2, entries 10–14), cyclic, and linear alkenes (Table 2, entries 16–20) under similar reaction conditions. Hydroxybromination of all olefins took place quickly and completed in less than or equal to 5 min.

Olefin with highly activated arenes, that is, 4-methoxystyrene produced the corresponding bromohydrin in excellent yield without the formation of ring or dibrominated products (Table 2, entry 2). Olefins with moderately activated arenes (alkyl substituted), that is, 4-methyl, 4-*tert*-butyl, and 2,4-dimethylstyrene yielded the corresponding bromohydrins in moderate to high yields without forming any side-chain and ring brominated products, but a significant amount of dibromo product was observed (Table 2, entries 3–5). α-Methylstyrene gave the respective bromohydrin in a 97% yield, whereas 4-chloro-α-methylstyrene afforded the corresponding bromohydrin in an 84% yield, along with a substantial amount (10%) of dibrominated product (Table 2, entries 8 and 9).

Regio- as well as stereoselective products were formed when asymmetric *trans*-alkenes were subjected to bromohydroxylation and selectively corresponding *erythro* isomers were obtained. *trans*-Cinnamyl alcohol provided the corresponding *erythro* bromohydrin in excellent yield (Table 2, entry 10). When the conjugated ketones, acids, and esters with a phenyl group at the β-position were subjected to bromohydroxylation under similar reaction conditions, furnished the corresponding *erythro*-β-hydroxy-α-bromo products accompanied by a significant amount of *erythro*-α,β-dibromo products (Table 2, entries 11–14).

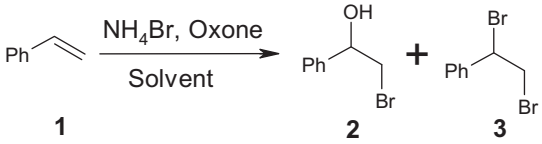
Not only aromatic olefins, cyclic, and linear olefins also gave the corresponding hydroxybrominated products in moderate to high yields (Table 2, entries 16–20). 1-Methyl-1-cyclohexene and 3-methyl-3-butene-1-ol exclusively yielded the Markovnikov's products (Table 2, entries 17 and 18), while with monosubstituted linear olefin, a limited *anti*-Markovnikov product was also observed. For example, 1-dodecene resulted in the formation of Markovnikov product (1-bromododecan-2-ol) as well as *anti*-Markovnikov product (2-bromododecan-1-ol) in 47% and 14% yields, respectively (Table 2, entry 19). Mixed regioselectivity is observed with linear asymmetric *trans*-alkene, that is, *trans*-2-octene afforded the *erythro*-2-bromooctan-3-ol and *erythro*-3-bromooctan-2-ol in the ratio of 25:36 (Table 2, entry 20).

Bromohydroxylation of electron-deficient double bond in 1,4-naphthoquinone and coumarin failed to react (Table 2, entries 21 and 22). The attempted bromohydroxylation of cholesterol and cholest-4-ene-3-one resulted in a complex mixture, which contained virtually no bromohydrin.



Scheme 1. Hydroxybromination and dibromination of olefins.

Table 1
Optimization of the bromohydrins and dibromides



Entry	Solvent	Time	Yield[a] (%)	
			2	**3**
1	CH_3CN	24 h[b]	—	60
2	Acetone	24 h[b]	2	48
3	DCM	24 h[b]	—	—
4	$CHCl_3$	24 h[b]	9	11
5	CCl_4	24 h[b]	—	—
6	H_2O	2 min[b]	56	29
7	CH_3CN/H_2O (9:1)	10 min[b]	65	30
8	CH_3CN/H_2O (4:1)	10 min[b]	84	12
9	CH_3CN/H_2O (3:2)	5 min[b]	85	10
10	CH_3CN/H_2O (1:1)	2 min[b]	92	5
11	CH_3CN/H_2O (2:3)	2 min[b]	83	12
12	CH_3CN/H_2O (1:4)	2 min[b]	79	16
13	DCM/H_2O (1:1)	3 min[b]	10	48
14	DCM/H_2O (1:1)	30 min[b]	10	49
15	$CHCl_3/H_2O$ (1:1)	3 min[b]	8	55
16	CCl_4/H_2O (1:1)	3 min[b]	12	40
17	Acetone/H_2O (1:1)	2 min[b]	85	10
18	CH_3CN	5 h[c]	—	65
19	CH_3CN	24 h[d]	—	80
20	CH_3CN	7 h[e]	—	97
21	CH_3CN/H_2O (10:0.25)	19 h[d]	13	81
22	CH_3CN/H_2O (10:0.5)	1.3 h[d]	20	73
23	CH_3CN/H_2O (10:1)	3 min[d]	33	60

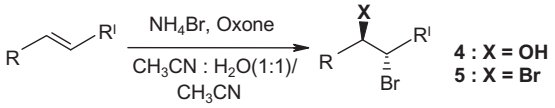
[a] Isolated yields.
[b] Styrene (2 mmol), NH_4Br (2.2 mmol), Oxone® (2.2 mmol), solvent (10 mL), rt.
[c] Reflux temperature.
[d] Styrene (2 mmol), NH_4Br (4.4 mmol), Oxone® (2.2 mmol), solvent (10 mL), rt.
[e] Reflux temperature.

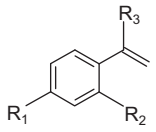
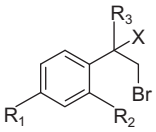
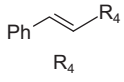
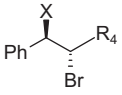
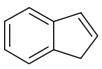
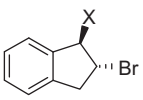
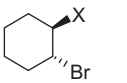
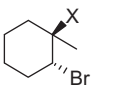
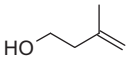
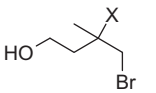
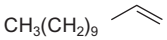
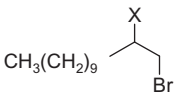
From the investigated results of bromohydroxylation of styrene in different solvents, we observed that acetonitrile turned out to be the best solvent for the formation of respective dibrominated product in terms of yield and reaction rates (Table 1, entry 1). Thus, we investigated the dibromination of styrene with NH_4Br and oxone® in CH_3CN and in combination with H_2O at room temperature and reflux temperature (Table 1, entries 18–23). One equivalent of styrene treated with 2.2 equiv of NH_4Br and 1.1 equiv of oxone® in CH_3CN at room temperature gave the corresponding dibrominated product with an 80% yield in 24 h (Table 1, entry 14). Significant improvement in yield and decrease in reaction time were achieved by conducting the reaction at reflux temperature and yielded the respective dibrominated product in a 97% yield within 7 h (Table 1, entry 20).

After optimizing the reaction conditions, we have extended the process to a variety of olefins, which are summarized in Table 2. They were conveniently converted into their respective dibromides in excellent yields (in exception 4-methoxystyrene and α-methylstyrene provided a mixture of unidentified products (Table 2, entries 2, 8 and 9)).

Dibromination of asymmetric *trans*-alkenes selectively formed the corresponding *erythro* isomers (Table 2, entries 10–14). Cyclic and linear alkenes furnished the corresponding dibrominated product in excellent yields (Table 2, entries 16–20). In case of 1,4-naphthoquinone, instead of the expected dibrominated product, 2-bromo-1,4-naphthoquinone was obtained in excellent yield (Table 2, entry 21).

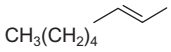
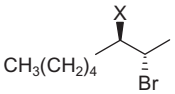
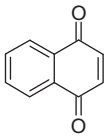
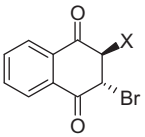
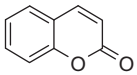
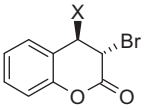
Table 2
Synthesis of Bromohydrins and Dibromides from Various Olefins



Entry	Olefin			Time	Product	Yield[a] (%)	
						4	5
							
	R_1	R_2	R_3				
1	H	H	H	2 min[b]		92 (**4a**)	5 (**5a**)
				7 h[c]		–	97 (**5a**)
2	OMe	H	H	1 min[b]		90 (**4b**)	–
3	Me	H	H	2 min[b]		79 (**4c**)	16 (**5c**)
				5 h[c]		–	95 (**5c**)
4	Me	Me	H	1 min[b]		70 (**4d**)	15 (**5d**)
				4 h[c]		–	92 (**5d**)
5	^{t}Bu	H	H	1 min[b]		66 (**4e**)	17 (**5e**)
				6 h[c]		–	0 (**5e**)
6	Cl	H	H	2 min[b]		89 (**4f**)	7 (**5f**)
				13 h[c]		–	96 (**5f**)
7	Br	H	H	3 min[b]		89 (**4g**)	6 (**5g**)
				13 h[c]		–	90 (**5g**)
8	H	H	Me	2 min[b]		97 (**4h**)	–
9	Cl	H	Me	2 min[b]		84 (**4i**)	10 (**5i**)
							
10	CH_2OH			3 min[b]		92[e] (**4j**)	5[e] (**5j**)
				12 h[c]		–	98[e] (**5j**)
11	$COCH_3$			3 min[b]		77[e] (**4k**)	15[e] (**5k**)
				15 h[c]		–	90[e] (**5k**)
12	COOH			3 min[b]		80[e] (**4l**)	10[e] (**5l**)
				13 h[c]		–	96[e] (**5l**)
13	COOMe			4 min[b]		63[e] (**4m**)	27[e] (**5m**)
				12 h[c]		–	97[e] (**5m**)
14	COPh			3 min[b]		62[e] (**4n**)	30[e] (**5n**)
				13 h[c]		–	97[e] (**5n**)
15				1 min[b]		86 (**4o**)	5 (**5o**)
				8.3 h[c]		–	90 (**5o**)
16				3 min[b]		85 (**4p**)	9 (**5p**)
				23 h[d]		–	96 (**5p**)
17				1 min[b]		89 (**4q**)	6 (**5q**)
				20 h[d]		–	93 (**5q**)
18				1 min[b]		84 (**4r**)	9 (**5r**)
				4 h[c]		–	89 (**5r**)
19				2 min[b]		47 (**4s**) (14)[f] (**4s^I**)	33 (**5s**)
				9 h[c]		–	97 (**5s**)

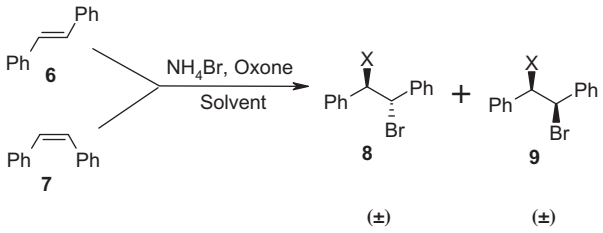
(*continued on next page*)

Table 2 (*continued*)

Entry	Olefin	Time	Product	Yield[a] (%)	
				4	5
20		1 min[b]		25[e] (**4t**) (36)[g] (**4t**[I])	30[e] (**5t**)
		5 h[c]		–	96[e] (**5t**)
21		1 h[b]		–	–
		5 h[c]		–	–(97)[h] (**5u**)
22		1 h[b]		–	–
		10 h[c]		–	23 (**5v**)

[a] Isolated yields.
[b] Olefin (2 mmol), NH_4Br (2.2 mmol), Oxone® (2.2 mmol), CH_3CN/H_2O (1:1) (10 mL) at room temperature.
[c] Olefin (2 mmol), NH_4Br (4.4 mmol), Oxone® (2.2 mmol), CH_3CN (10 mL) at reflux temperature.
[d] At room temperature.
[e] Only *erythro* products.
[f] 2-Bromododecan-1-ol.
[g] *erythro*-3-Bromooctan-2-ol.
[h] 2-Bromo-1,4-naphthoquinone.

Table 3
Hydroxybromination and Dibromination of *cis* and *trans*-stilbene



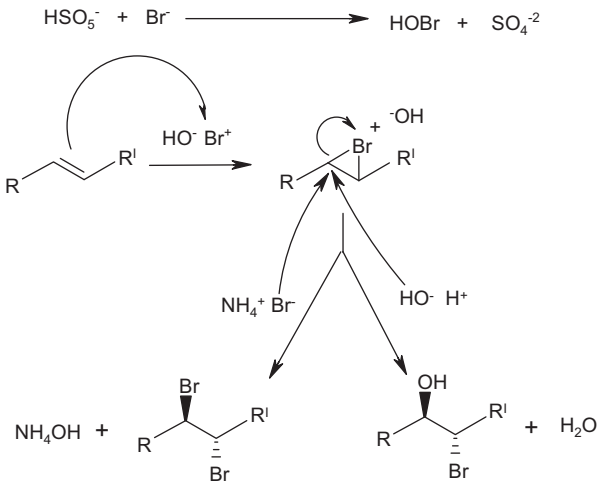
Entry	Stilbene	Solvent	Time	X	Yield (%)[a]	
					8	**9**
1	**6**	CH_3CN/H_2O (1:1)	5 min[b]	OH	78 (**8a**)[d]	–
2	**7**	CH_3CN/H_2O (1:1)	2 min[b]	„	15[d] (**8a**)	51[f] (**9a**)
3	**6**	CH_3CN	20 h[c]	Br	80[e] (**8b**)	–
4	**7**	CH_3CN	16 h[c]	„	–	95[f] (**9b**)

[a] Isolated yields.
[b] Stilbene (2 mmol), NH_4Br (2.2 mmol), Oxone® (2.2 mmol), Solvent (10 mL) at room temperature.
[c] Stilbene (2 mmol), NH_4Br (4.4 mmol), Oxone®2.2 mmol), Solvent (10 mL) at room temperature.
[d] *erythro* Products.
[e] *meso* Product.
[f] *threo* Products.

The role of alkene geometry on the *anti* stereochemistry of the addition was tested by conducting reactions with *cis* and *trans*-stilbene. Hydroxybromination and dibromination of *cis*-stilbene were more rapid than its *trans*-isomer and both gave *anti* addition products. *trans*-Stilbene produced *erythro* hydroxybrominated (Table 3, entry 1) and *meso* dibrominated products (Table 3, entry 3), whereas *cis*-stilbene afforded the corresponding *threo* dibrominated product (Table 3, entry 4) (In case of hydroxybromination of *cis*-stilbene, significant amount of corresponding *erythro* isomer was also obtained (Table 3, entry 2)).

To study the mechanism of the reaction (hydroxybromination/dibromination), we carried out a blank experiment with styrene and NH_4Br in the absence of oxone® under similar reaction conditions and the reaction did not succeed. Thus, the role played by the oxone® (oxidant) was justified. The plausible reaction mechanism for hydroxybromination and dibromination of olefins is shown in Scheme 2 based on the literature[18] and blank experiment. It is assumed that oxidation of bromide ion by peroxymonosulfate ion could give the hypobromite ion, which further undergoes electrophilic addition onto the olefin to give a three-membered cyclic bromonium ion intermediate. The cyclic intermediate undergoes ring opening by the nucleophile (hydroxy or bromide ion) via S_N2 path way to yield the *anti* vicinal hydroxybromo/dibromo substituted product. The S_N2 opening is responsible for high anti-stereoselectivity of the bromo product. In all aromatic olefins, the incoming nucleophile entered at the benzylic position of cyclic intermediate exclusively. The regioselectivity (of aromatic olefins) can be explained by considering the fact that the α-position (benzylic) is more positive than the β-position due to the presence of the aromatic ring. Nucleophilic opening of the cyclic bromonium intermediate is most likely from the more positive α-position. The stereochemistry of the products is confirmed by comparing the ^1H NMR coupling constant data of protons attached to the carbons bearing –OH/–Br and –Br groups of the bromohydrins/dibromides with previously reported data.[6–8,19]

In conclusion, we have developed a mild and efficient method for the regio- and stereoselective hydroxybromination and dibromination of olefins using eco-friendly reagents in environmentally benign and non-chlorinated solvents. Though oxone® is known as a best reagent (oxidant) for the epoxidation of olefins, we have not observed any epoxidation products in this investigation. The advantage of our system over other methods is that the use of a catalyst is not required to enhance the reactivity of the reagents, to control the regio- and stereoselectivities or to improve the yield. The products are easily separated from the reagents and their



Scheme 2. The plausible reaction mechanism.

byproducts. It is noteworthy that the present method provides a new route for the bromohydroxylation of olefins.

Acknowledgment

M.A.K. thanks the CSIR, New Delhi, for the award of a Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.026.

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16. General procedure for the synthesis of bromohydrins: To a solution of olefin (2 mmol) in CH_3CN/H_2O (1:1) (10 mL) were added NH_4Br (2.2 mmol) and Oxone® (2.2 mmol) and the mixture was stirred at room temperature for the time shown in Table 2. After completion (as indicated by TLC), the reaction mixture was filtered and the solvent evaporated under reduced pressure. The products were purified by column chromatography (Hexane/EtOAc, 90:10) over silica gel.
17. General procedure for the synthesis of dibromides: To a solution of olefin (2 mmol) in CH_3CN (10 mL) were added NH_4Br (4.4 mmol) and Oxone® (2.2 mmol) and the mixture was stirred at reflux temperature for the time shown in Table 2. After completion (as indicated by TLC), the reaction mixture was filtered and the solvent evaporated under reduced pressure. The products were purified by column chromatography (Hexane/EtOAc, 98:2) over silica gel.
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