Tetrahedron 65 (2009) 2791–2797

Contents lists available at ScienceDirect

Tetrahedron

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

Comparative study of the vicinal functionalization of olefins with 2:1 bromide/bromate and iodide/iodate reagents

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ARTICLE INFO

Article history:
Received 7 November 2008
Received in revised form 27 January 2009
Accepted 28 January 2009
Available online 4 February 2009

Keywords:
Bromide/bromate
Iodide/iodate
Reagent
Olefins
Functionalization

ABSTRACT

A comparative evaluation was made on the syntheses of vicinal halohydrins, halo methyl ethers, and halo acetates from olefins using 2:1 Br^-/BrO_3^- and I^-/IO_3^- reagents. In many cases both reagents afforded products selectively in high yields. The highest halogen atom efficiencies attained were 97% and 93% for Br^-/BrO_3^- and I^-/IO_3^-, respectively. Of the two reagents, I^-/IO_3^- was established to be the preferred reagent for vicinal functionalization of linear alkenes and also for halo acetate preparation. However, only Br^-/BrO_3^- was effective for vicinal functionalization of *trans*-stilbene and chalcones.

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1. Introduction

Vicinal functionalization of olefins is an important synthetic tool especially when the reaction affords products in regio- and stereoselective manner.[1] Vicinal halohydrins, halo ethers, and halo esters are versatile synthetic intermediates that provide access to an array of functional groups.[2]

A large number of reagents such as *N*,*N*-dibromobenzene sulphonamide,[1] 'selectfluor'-K/KBr,[3] *p*-nitrobenzene-sulphonyl peroxide/Br^-,[4] tribromoisocyanuric acid,[5] Ag^+/Br_2,[6] NBS/acid/MeOH,[7] and 1,3-dibromo-5,5-dimethylhydantoin (DDH)/MeOH[8] have been reported for synthesis of halo methyl ethers. Alkali halide salts, in combination with IO_4^- and LDH-WO_4^{2-} as oxidizing agents—which generate the halonium ion—have also been reported for preparation of chloro- and bromo-derivatives.[9] Heasley has reported the BF_3-promoted reaction of methyl hypochlorite and methyl hypobromite with olefin to obtain fluoro chloride and fluoro bromide derivatives.[10] Methoxy halides were obtained as side products.

Preparation of iodohydrins, iodo methyl ethers, and iodo acetates using *N*-iodosuccinimide (NIS)[7b,11] and bis(pyridine)-iodine(I)tetrafluoroborate[12] has been reported. I_2/H_2O has also been used successfully in synthesis of iodohydrins and iodo ethers, especially cyclic ethers, from the corresponding olefins.[13] Vicinal functionalization with $I_2/CuO\cdot HBF_4$,[14] I_2/Cu(II)acetate,[15] I_2/Ag(I)carboxylate,[16] I_2/sulfolane,[17] I_2/Pb(II) acetate,[18] and I_2/EPZ-10[19] has also been reported. Cornforth and Green used dilute aqueous solution of iodic acid to oxidize iodide back to iodine and applied the methodology to obtain iodohydrin and propylene oxide from propene.[20] Among hypervalent iodine-containing reagents, $H_5IO_6/NaHSO_3$ has been used wherein the two components of the reagent participate in a redox process to generate the desired reactive iodonium species.[21]

The halide–halate reactions (X=Br, I) in water represented by Eq. 1 are well known. The one involving iodine is referred to as the Dushman reaction,[22] and finds useful applications in analysis, while the reaction involving bromine is known to play an important role in oscillating chemical reactions.[23] The mechanistic pathways for the reactions are complex and as yet not fully understood.

$$XO_3^- + 5X^- + 6H^+ \rightarrow 3X_2 + 3H_2O \qquad (1)$$

The rate equation (*r*=rate) can be expressed in the form of Eq. 2.[24,25] (The rate equation is still more complex in presence of other solution species such as acetate ion.) The second term is important at low concentrations of halide ion but can be ignored otherwise. The values of k_1 for the Br^-/BrO_3^- and I^-/IO_3^- systems are reported to be 0.81 $M^{-4}\,s^{-1}$ and $1.3\times10^9\ M^{-4}\,s^{-1}$, respectively. In view of the second order dependence on $[H^+]$, the reactions can be activated only in presence of acid. However, since the rate constant of the I^-/IO_3^- reaction is nine orders of magnitude higher than that of the Br^-/BrO_3^- reaction, the former reaction is fast even under mildly acidic conditions.

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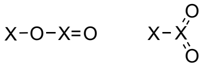
doi:10.1016/j.tet.2009.01.095

$$r = k_1\left[XO_3^-\right]\left[H^+\right]^2\left[X^-\right]^2 + k_2\left[XO_3^-\right]\left[H^+\right]^2\left[X^-\right] \quad (2)$$

The formation of the asymmetric intermediate X_2O_2 has been implicated in the mechanism of Eq. 1. The asymmetric structures shown below were proposed originally for Cl_2O_2 by Taube and Dodgen.[26] X_2O_2 is obtained from the reactions of Eq. 3. It can undergo the further reactions of Eqs. 4–6.



$$XO_3^- + H^+ \rightarrow XO_3H \quad (3a)$$

$$XO_3H + X^- + H^+ \rightarrow X_2O_2 + H_2O \quad (3b)$$

$$X_2O_2 + H_2O \rightarrow XO_2H + XOH \quad (4)$$

$$XO_2H + X^- + H^+ \rightarrow 2XOH \quad (5)$$

$$XOH + X^- + H^+ \rightarrow X_2 + H_2O \quad (6)$$

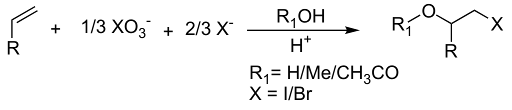
We have shown through recent studies that 2:1 Br^-/BrO_3^- is a useful reagent in bromine substitution reactions.[27–30] The reagent can be obtained readily from the intermediate of liquid bromine manufacture thereby eliminating liquid bromine from the product life cycle. The overall stoichiometry of the reaction is depicted by Eq. 7.

$$3RH + XO_3^- + 2X^- + 3H^+ \rightarrow 3RX + 3H_2O \quad (7)$$

The rationale for selecting the 2:1 ratio was to avoid the reaction of Eq. 6 and, instead, to effect the reaction with high bromine atom efficiency employing the reactive intermediates formed in Eqs. 3–5. A few studies were also undertaken with 2:1 I^-/IO_3^-. Although our efforts were largely focused on substitution reactions, preliminary studies were carried out to produce halohydrins from olefins with the above reagents. Unfortunately, the reactions were found to generate sizable amounts of impurities such as dihalo products. We report herein our studies aimed at developing a clean and efficient protocol for vicinal functionalization of olefins with the above reagents. We have also undertaken a systematic study comparing the Br^-/BrO_3^- and I^-/IO_3^- reagents. The study was considered to be of interest in view of the large difference in the values of k_1 in Eq. 2 for the two halogens and the behavioral difference between the halonium ion intermediates.

2. Results and discussion

Scheme 1 is the general representation of vicinal functionalization of olefins with the 2:1 X^-/XO_3^- acid-activated reagents studied in the present work. In our previous attempt to produce halohydrin, experiments were carried out by adding acid gradually into the flask containing all of the substrate and reagent. Since this mode of addition led to substantial formation of dihalo impurity,[30]



Scheme 1. Vicinal functionalization of olefins through in-situ acid activation of the 2:1 X^-/XO_3^- couple.

Table 1
Synthesis of halohydrins from olefins

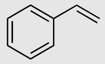
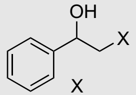
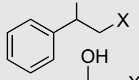
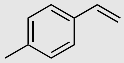
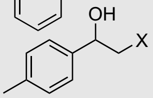
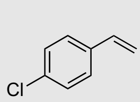
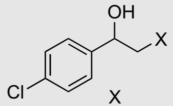
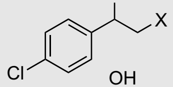
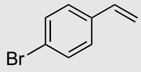
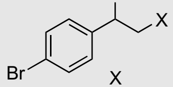
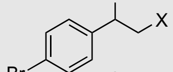
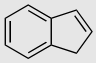
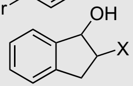
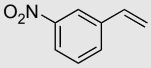
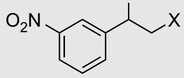
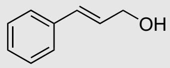
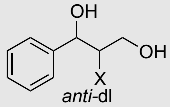
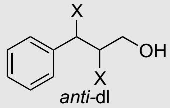
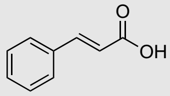
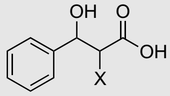
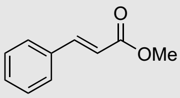
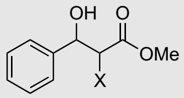
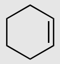
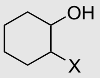
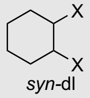
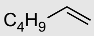
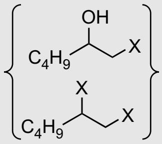
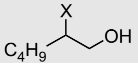
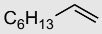
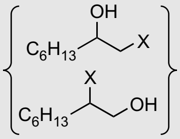
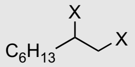
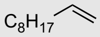
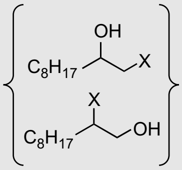
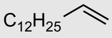
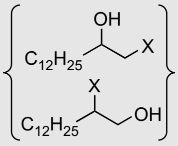
Entry	Substrate	Product(s)	X	Time (h)	Yield[a] (%)
1			Br	0.5	86[30b] (05)[b]
2			I	2.0	92[30a]
3			Br	0.5	97[30b]
4			I	2.0	87[30a]
5			Br	0.5	74 (11)[b]
6			I	2.5	84
7			Br	0.5	74[7a] (13)[b]
8			I	3.0	80
9		 syn-dl	Br	0.5	93[7a]
10			I	2.0	CNI[c]
11			I	2.0	88
12		 anti-dl	Br	0.5	74[7a] (10)[b]
13		 anti-dl	I	2.0	93
14		 anti-dl	Br	0.5	68[7a]
15			I	2.0	79[33]
16		 anti-dl	Br	1.0	60
17			I	2.5	93
18[d]		 syn-dl	Br	0.5	84[30b] (04)[b]
19[d]		 syn-dl	I	2.0	83[30a]
20[d,e]			Br	0.5	71[30b] (10)[b]
21[d,e]			I	2.0	86[30a]

Table 1 (*continued*)

Entry	Substrate	Product(s)	X	Time (h)	Yield[a] (%)
22[e]			Br	0.5	69[30b] (10)[b]
23[e]			I	2.0	75[30a]
24[e]			I	3.0	77
25[e]			I	3.0	92

[a] Unless specified otherwise, yield refers to total isolated yield of halohydrin.

[b] Yield in parentheses is that of isolated yield of dihalo impurity (note that for all entries where dihalo impurity is not shown it implies that no dihalo impurity was isolated).

[c] Desired product observed in GC–MS of crude but could not be isolated.

[d] Four fold excess of substrate was taken.

[e] 1-Halo and 2-halo regioisomers were obtained in 82:18, 100:0, 72:28, 100:0, 98:2 and 79:21 ratios in the crude reaction mixtures of entries 20–25. Note that for all other entries only single regioisomer was isolated.

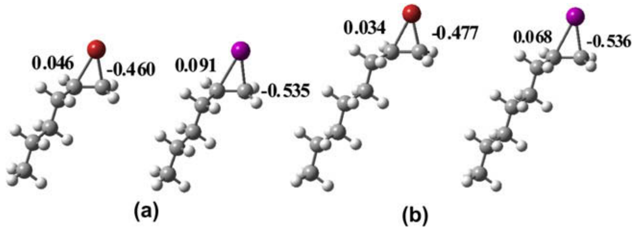


Figure 1. MP2/LACVP* optimized three-membered cyclic bromonium (red) and iodonium (purple) intermediates with (a) 1-hexene and (b) 1-octene, respectively. The calculated natural charges for C1 and C2 are indicated.

we ascribed this to the competing pathway of Eq. 6, which would be inevitable in presence of large excess of halide ion and, particularly, if the reactions of Eqs. 3–5 are slow compared to the reaction of Eq. 6. The problem was mitigated by reversing the addition sequence, i.e., stoichiometric amount of acid was taken in a single lot in the flask along with olefin and the reagent was added gradually. Further, to suppress polymerization under the prevailing acidic condition when reverse addition was followed, the solvent system was changed to DMSO–water in the ratio 3:1 (v/v). This solvent system was also advantageous in as much as it inhibited over-oxidation. The improved procedure was tested initially on styrene (entries 1 and 2, Table 1). 2-Bromo-1-phenylethanol and 2-iodo-1-phenylethanol were obtained in 86% and 92% isolated yields, respectively, compared to 79% and 57% obtained previously.[30] Dibromo impurity was 4.5% whereas the corresponding diiodo impurity was not seen at all. The experiment of entry 2 was also carried out at 15.3 g scale and the column-purified product was obtained in 90.7% yield. The study was extended to several other olefins and high yields of desired products were obtained consistently as can be seen from Table 1. The substrate to reagent mole ratio was 1:1 in all cases except for the reactions with cyclohexene and 1-hexene for which fourfold excess of substrate was taken (entries 18–21). It can be seen from the table that the highest bromine atom efficiency was 97% (entry 3) while the highest iodine atom efficiency was 93% (entries 13 and 17). The apparently longer reaction time with I^-/IO_3^- arose mainly due to the fact that the reactions of Eqs. 3–6 are extremely fast when mineral acid is used and the iodonium intermediates may not have sufficient time to react fully with the organic substrate. The iodine, too, reacts with the substrate, albeit more slowly (this was confirmed through independent studies with $I_2/KIO_3/H^+$), and this necessitates more gradual addition of the reagent. With Br^-/BrO_3^- build up of bromine color was negligible as the bromonium intermediate presumably is sufficiently long lived to react with the olefin. Any Br_2, which is generated in the side reaction of Eq. 6, would also react instantaneously with the substrate. Hence the reagent could be added faster. It can be seen from Table 1 that both reagents give similar yields for a large number of reactions. However, although dibromo formation was greatly suppressed, it nonetheless occurred in several reactions whereas diiodo formation was not seen at all.[31] Since the desired reactions presumably proceed via formation of the halonium intermediates, regioselectivity is expected to be controlled by the charge differences between the two carbon centers in the three-membered cyclic intermediates.[32] Accordingly, computational studies were undertaken with 1-hexene and 1-octene (Fig. 1). The computed MP2/LACVP* results showed that the bromonium and iodonium intermediates are unsymmetrical in nature, the natural charges on C1 and C2 being negative and positive, respectively, for both bromonium [C1: −0.460 (1-hexene), −0.477 (1-octene); C2: +0.046 (1-hexene), +0.034 (1-octene)] and iodonium [C1: −0.535 (1-hexene), −0.536 (1-octene); C2: +0.096 (1-hexene), +0.068 (1-octene)] cases. The greater polarization of charges in iodonium ion intermediates suggests that the regioselectivity would be higher compared to that of bromonium ion intermediates, in line with the experimental observations.

The method was extended to the preparation of halo methyl ethers from olefins. The reagent to substrate mole ratio was 1.1:1 in all cases. Acid activation of the X^-/XO_3^- reagent in methanol was carried out with 98% sulfuric acid to provide protons under nearly dry condition and thereby suppress halohydrin formation. (Note that since the acid is consumed in the reaction, the solution has negligible acidity at the end of the reaction.) When styrene was subjected to reaction with 2:1 $[Br^-]/[BrO_3^-]$ and $[I^-]/[IO_3^-]$, respectively, through in-situ acid activation in methanol at 0–10 °C, (2-bromo-1-methoxyethyl)benzene and (2-iodo-1-methoxyethyl)benzene were each obtained in 94% isolated yield (entries 1 and 2, Table 2). A series of substrates were subjected to the halo methyl ether syntheses and high yields of the corresponding bromo and iodo derivatives were obtained in most cases. With stilbene and chalcone as substrates, the bromo methyl ethers were formed in 89% and 97% isolated yields, respectively (entries 13 and 21), but the reactions were unsuccessful with the iodo reagent. When (*E*)-1-(pyridin-2-yl)-3-*p*-tolylprop-2-en-1-one and 4-methoxy chalcone were subjected to bromoetherification reaction, the desired products were obtained in 47% and 79% yields, respectively (entries 23 and 25) with *anti*/*syn* addition ratios of 1:0.5 and 1:0.58, respectively, as estimated from NMR spectra. As in the case of chalcone, the corresponding iodoetherification reactions were unsuccessful and the desired iodo ether products could not be isolated (entries 24 and 26). Methyl cinnamate gave high yields of bromo ether as well as iodo ether (entries 17 and 18). Indene and cyclohexene gave good-to-moderate yields of the bromo and iodo methyl ethers (entries 11 and 12, 27 and 28, Table 2). As in the case of 1-hexene and 1-octene (Fig. 1), the computed MP2/LACVP* results for indene show that the bromonium and iodonium intermediates are unsymmetrical in nature. The charge density on the α-carbon is positive in both cases (I, 0.195; Br, 0.086) whereas the corresponding charge density on the β carbon is negative (I,

Table 2
Synthesis of halo methyl ethers from olefins

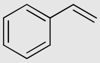
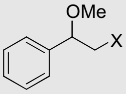
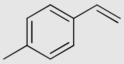
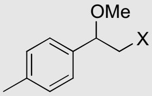
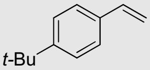
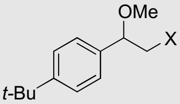
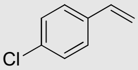
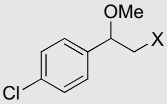
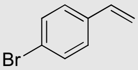
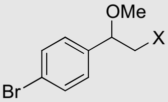
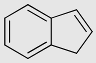
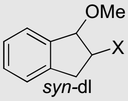
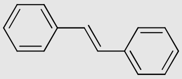
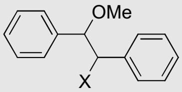
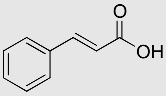
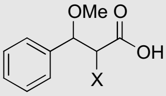
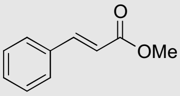
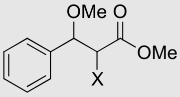
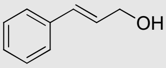
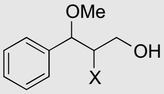
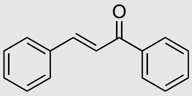
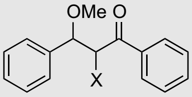
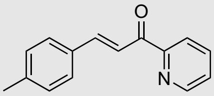
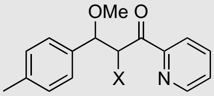
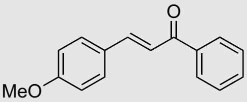
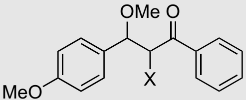
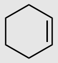
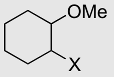
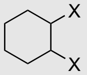
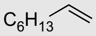
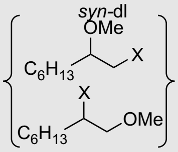
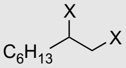
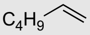
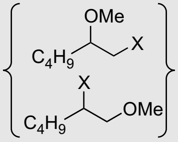
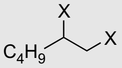
Entry	Substrate	Product(s)	X	Time (h)	Yield[a] (%)
1			Br	2.5	94[7c]
2			I	0.75	94
3			Br	2.5	93[7c]
4			I	0.6	95
5			Br	3.0	99
6			I	1.0	92
7			Br	2.5	93[1]
8			I	1.0	89
9			Br	2.5	96[7a]
10			I	1.0	91
11		 *syn*-dl	Br	2.0	86[7a]
12			I	0.5	92
13		 *anti*-dl	Br	3.0	89[3]
14			I	3.0	0
15		 *anti*-dl	Br	3.0	90
16			I	1.2	81
17		 *anti*-dl	Br	2.5	97[1,7a]
18			I	2.0	94
19		 *anti*-dl	Br	3.0	99[7c]
20			I	1.25	89
21		 *anti*-dl	Br	1.0	97
22			I	0.65	0
23[b]		 *anti*-dl + *syn*-dl	Br	2.0	47
24			I	2.0	0
25[b]		 *anti-dl* + *syn-dl*	Br	3.0	79
26			I	2.0	0

Table 2 (*continued*)

Entry	Substrate	Product(s)	X	Time (h)	Yield[a] (%)
27		 *syn*-dl	Br	2.5	69[7c] (09)[c]
28		 *syn*-dl	I	0.65	78
29			Br	2.5	79[d,7c] (10)[c]
30			I	1.20	65[d]
31			Br	2.5	81[d,7c] (15)[c]
32			I	2.5	89[d]

[a] Unless specified otherwise, yield refers to isolated yield of halo methyl ether.

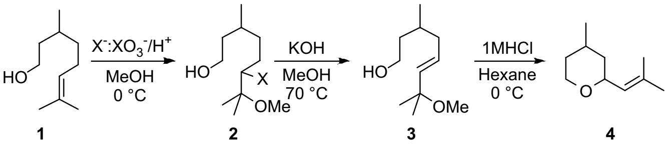
[b] *anti*/*syn* ratio was 1:0.5 and 1:0.58 in entries 23 and 25, respectively (estimated from NMR).

[c] Yield in parentheses is the yield (GC–MS area %) of dihalo impurity (note that for all entries where dihalo impurity is not shown it implies that no dihalo impurity was observed).

[d] Ratios of 1-halo and 2-halo regioisomers were 79:21, 89:11, 83:17 and 91:9 in the crude reaction mixtures of entries 29, 30, 31 and 32, respectively (by GC–MS).

−0.642; Br, −0.179), which explains the high regioselectivity observed in both reactions. Proton NMR data of the 2-bromo-1-methoxy indane isolated from the reaction indicated that the bromo methoxy addition reaction was antiselective as evident from the low coupling constant of the vicinal hydrogens.[32] With 1-octene and 1-hexene as substrates, the isolated yields of the corresponding bromo methyl ethers were 79% and 81%, respectively (entries 29 and 31), whereas a similar reaction on iodo-methoxy-addition to 1-octene gave a lower yield of 65% but with higher regioselectivity toward the 1-halo-2-methoxy derivative [79:21 vs 89:11 for Br and I, respectively (entries 29 and 30)] as in the case of the corresponding halohydrin syntheses. The highest halogen atom efficiencies based on the data of Table 2 were 90% (entries 5 and 19) and 86% (entry 4) for Br^-/BrO_3^- and I^-/IO_3^-, respectively. We also synthesized the bromo methoxy derivative of citronellol (**1**) and utilized it toward synthesis of rose oxide (**4**) in one pot in 66% overall yield (Scheme 2). When the synthesis was carried out via the iodo-methoxy derivative, the product was obtained in 82% yield.[8] We thereafter extended the study to the syntheses of halo acetates from olefins employing the 2:1 X^-/XO_3^- reagent (Table 3). Acetic acid served the triple role of proton source, nucleophile and solvent in these reactions.

The reagent to substrate mole ratio was 1.1:1 in all cases. As can be seen from the table, the yields of the bromoacetates were generally poor (32–44%), with pronounced formation of dibromo impurity. In contrast, the iodo acetate derivatives of the same olefins were achieved cleanly and in high yields (68–98%) in all the reactions where direct comparison was possible. The maximum iodine atom efficiency was found to be 89% (entry 4) whereas the maximum bromine atom efficiency for desired product was only 40%. We ascribe the results to the large variation in k_1 (Eq. 2), which enables the reaction of I^-/IO_3^- to proceed satisfactorily even with mild acids whereas Br^-/BrO_3^- requires stronger acidic conditions. BrOH which may form would not only see the substrate but also Br^- in solution, leading to Br_2 formation and build up of dibromo impurity. As in the case of halo ether preparation, the iodo acetate of stilbene proved elusive while the corresponding bromo derivative could be obtained albeit in low (36%) yield. The iodoesterification reactions attempted with methyl cinnamate and 4-methoxy chalcone were also unsuccessful.

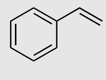
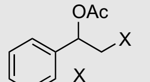
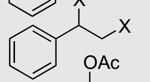
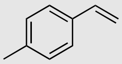
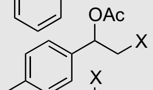
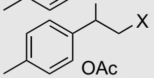
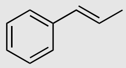
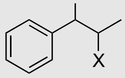
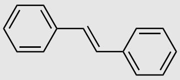
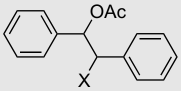
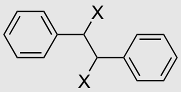
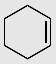
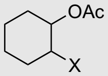
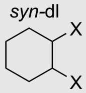
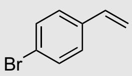
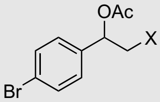
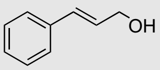
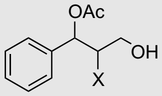


Scheme 2. Single pot synthesis of rose oxide from citronellol via halo methyl ether.

3. Conclusions

In conclusion, we have demonstrated the utility of 2:1 acid-activated X^-/XO_3^- couple for the efficient syntheses of a wide range of halohydrins, halo methyl ethers and halo acetates from olefins with high selectivity in most cases. Although in the present work the reagents were formulated from the pure salts, these are readily prepared in cost-effective manner and exhibit high halogen atom efficiency.[29] The highest halogen atom efficiencies attained in the present work were 97% and 93% for Br^-/BrO_3^- and I^-/IO_3^-, respectively. Other than acid activation, no catalyst was required, as such. Br^-/BrO_3^- and I^-/IO_3^- gave similar results in most of the halohydrin and halo-methoxy-addition reactions studied. For reactions with linear terminal olefins, the regioselectivity was found to be better with the iodo reagent and is ascribed to the larger difference in the charge densities of the C1 and C2 carbons in the three-membered cyclic iodonium intermediate. Besides the greater regioselectivity, another advantage of I^-/IO_3^- was the complete elimination of diiodo impurity formation. The reagent also proved superior in the synthesis of rose oxide from citronellol. I^-/IO_3^- was also found to be a superior reagent for preparation of halo acetates from olefins and this is ascribed to the facile formation of I^+ from I^- and IO_3^- even under mild acidic conditions such as that encountered

Table 3
Synthesis of halo acetates from olefins

Entry	Substrate	Product(s)	X	Time (h)	Yield[a] (%)
1			Br	6.0	42 (35)[b]
2			I	3.5	98
3			Br	6.0	44 (35)[b]
4			I	3.0	96
5		 *anti*-dl	I	5.0	68
6		 *anti*-dl  *anti*-dl	Br	6.0	36 (22)[b]
7		 *syn*-dl	Br	6.0	32 (43)[b]
8		 *syn*-dl	I	3.0	89
9			I	3.0	89
10		 *anti*-dl	I	3.0	91

[a] Unless specified otherwise, yield refers to isolated yield of halo acetate.
[b] Yield in parentheses is the isolated yield of dihalo impurity (note that for all entries where dihalo impurity is not shown it implies that no dihalo impurity was isolated).

with use of acetic acid as nucleophile-cum-proton source. In all of the reactions studied, *trans*-stilbene and chalcones did not give the iodo ethers with I^-/IO_3^- whereas high yields of the bromo ethers were achieved with Br^-/BrO_3^-. Thus with both reagents having their respective merits, the two together offer a useful protocol for vicinal functionalization of olefins. The salt which precipitates in the course of the reaction comprises the counter cation of the reagent and the counter anion of the acid. If these are selected suitably in the halohydrin and halo ether preparations, one can ensure that the by-product salt also finds useful applications.

4. Experimental section

4.1. General

All the reagents used were analytical reagents purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded on a spectrometer operating at 200 and 50 MHz, respectively, in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in parts per million relative to the appropriate standard, and TMS as internal standard for ^1H and ^{13}C NMR spectra. GC–MS analyses were carried out on a Shimadzu GCMS-QP2010 instrument. A Restake Bellfonte's RTX-5 30 m×0.25 mm×0.25 μm column was used for the analysis with a helium carrier gas flow of 1.0 mL min^{-1}. The GC oven was held at 40 °C for 3 min and then ramped at 10 °C/min to 240 °C where it was held for 10 min. A 0.4 μL injection with a 1:30 split was used throughout. MS conditions: CI reagent gas was methane at a source pressure of 1 kg. The instrument was calibrated using PFTBA reference for CI with the CI reagent gas removed in CI mode. Mass spectra were acquired over the range *m*/*z* 85–400 with an acquisition time of 0.5 s and an inter-scan delay of 0.05 s. The data were processed using the GC–MS Real-timer. Microanalysis was carried out on a Perkin–Elmer 2400 instrument. Wherever possible, the analytical data were matched against reported data.

4.2. General procedure for synthesis of halohydrins [2-iodo-1-phenylethanol (entry 2, Table 1)]

Styrene (1.00 g, 9.61 mmol) and DMSO (12 mL) were taken in 50 mL round bottomed flask and stirred in water bath at 70–80 °C. To the above solution, stoichiometric amount of H_2SO_4 (4.8 mmol in 3 mL water) was added, followed by addition of stoichiometric amount of solid KI/KIO_3 [6.44 mmol KI+3.26 mmol KIO_3] in portions over a period of 30 min under vigorous magnetic stirring. The progress of the reaction was monitored by TLC. Stirring was continued for an additional 1.5 h under the same conditions. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with dilute solutions of $NaHCO_3$, $Na_2S_2O_3$ and brine. Finally it was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude product, which was purified by column chromatography on silica gel to afford the pure 2-iodo-1-phenylethanol (2.18 g, 8.8 mmol) in 92% yield. Similar procedure was employed for synthesis of bromohydrins listed in Table 1 using bromide/bromate with required quantity of acid.

4.2.1. Scale up of the reaction of entry 2, Table 2

Styrene (15.3 g, 147.1 mmol) and DMSO (80 mL) were taken in 250 mL round bottomed flask and stirred in water bath at 70–80 °C. To the above solution, H_2SO_4 (88.3 mmol in 25 mL water) was added, followed by addition of solid KI/KIO_3 [98.5 mmol KI+53.8 mmol KIO_3] in portions over a period of 45 min under vigorous magnetic stirring. The progress of the reaction was monitored by TLC. Stirring was continued for an additional 2.0 h under the same conditions. The reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layer was washed with dilute $Na_2S_2O_3$, dried over anhydrous Na_2SO_4 and the solvent stripped off under reduced pressure to get crude product, which was purified by column chromatography on silica gel to afford 33.1 g (133.5 mmol, 90.7% yield) of pure 2-iodo-1-phenylethanol.

4.3. General procedure for synthesis of halo methyl ethers [1-(2-iodo-1-methoxyethyl)-4-methyl-benzene (entry 4, Table 2)]

4-Methyl styrene (1.00 g, 8.47 mmol) and MeOH (10 mL) were taken in 50 mL round bottomed flask cooled with 5–10 °C water taken in a water bath. To the above solution, 8.47 mmol of concd H_2SO_4 was added slowly, followed by addition of 1.1 equiv of solid KI/KIO_3 [6.09 mmol KI+3.05 mmol KIO_3] in portions over a period of 30 min under vigorous magnetic stirring. The progress of the reaction was monitored by TLC. Stirring was continued for an additional 35 min under the same conditions. The solvent was removed under reduced pressure. Water was added to dissolve inorganic salts present in the residue and thereafter the residue was extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with dilute solutions of $NaHCO_3$, $Na_2S_2O_3$ and brine. Finally it was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude product, which was purified by column chromatography on silica gel to afford the pure 1-(2-iodo-1-methoxyethyl)-4-methyl-benzene (2.23 g, 8.09 mmol) in 95% yield. Similar procedure was employed for synthesis of bromo methyl ethers listed in Table 2 using bromide/bromate with required quantity of acid.

4.4. General procedure for synthesis of halo acetates [2-iodo-1-phenyl-ethyl ester (entry 2, Table 3)]

Styrene (1.00 g, 9.61 mmol) and acetic acid (20 mL) were taken in 50 mL round bottomed flask and 1.1 equiv of solid KI/KIO_3 [6.92 mmol KI+3.55 mmol KIO_3] added in portions over a period of 30 min under vigorous magnetic stirring at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (3.5 h) the solvent was removed at 60–65 °C under reduced pressure, the crude residue was treated with water and the product extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with dilute solutions of $NaHCO_3$, $Na_2S_2O_3$ and brine, followed by drying over anhydrous Na_2SO_4 and concentration under reduced pressure to get acetic acid 2-iodo-1-phenyl-ethyl ester (2.73 g, 9.41 mmol) in 98% yield. Similar procedure was employed for synthesis of other iodo acetates. The same procedure was also followed for the syntheses of bromoacetates listed in Table 3 using the corresponding bromide/bromate salt in acetic acid.

4.5. General procedure for one pot synthesis of rose oxide

Citronellol (1.56 g, 10.0 mmol) and MeOH (20 mL) were taken in 50 mL round bottomed flask and the contents were stirred at 5–10 °C. To the above solution, 5.5 mmol of concd H_2SO_4 was added slowly followed by the addition of 1.1 equiv of solid KI/KIO_3 [7.2 mmol KI+3.7 mmol KIO_3] in portions over 30 min under vigorous stirring at 5–10 °C. The progress of the reaction was monitored by TLC and no starting material was left after 2.5 h. Solid KOH (0.9 g, 16.0 mM) was then added into the same flask under stirring and once dissolution was complete the contents were refluxed for 2.5 h. The solvent was removed under reduced pressure. 10 mL of hexane and 10.0 mL of 1.2 N HCl were then added into the flask and the contents stirred at 0 °C for 3 h. The organic and aqueous layers were separated and aqueous layer was extracted once with 25 mL of dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by column chromatography on silica gel to obtain 1.263 g (8.20 mmol, 82% yield) rose oxide. The product was characterized by ^1H and ^{13}C NMR, IR and GC–MS.

4.6. Computational methods

All calculations were performed with the Spartan' 06 version, using MP2 electron correlated method.[34] Pseudopotential (LACVP*) and 6-31G* basis sets were used for the calculations.[35] All species were fully optimized with these basis sets, and harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. The natural population analysis was performed with NBO method.[36]

Acknowledgements

We thank Dr. P. Paul, Mr. V. P. Boricha, Mr. H. Brahmbhatt and Mr. V. Agrawal of our Analytical Division for analyses and Dr. A. Das for a sample of the chalcone used in Entry 23/24 of Table 2. We are also grateful to Dr. P. Ray and Dr. B. C. Ranu for helpful discussions and to the referees for their valuable suggestions. M.K.A. wishes to thank UGC, New Delhi for support under UGC-NET fellowship.

Supplementary data

Electronic supplementary information (ESI) on ^1H and ^{13}C NMR data, elemental analysis (of solid products) and NMR spectra/GC–MS of synthesized compounds is available free of charge. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.095.

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