A Convenient Halogenation of α,β-Unsaturated Carbonyl Compounds with *OXONE*® and Hydrohalic Acid (HBr, HCl)

Kyoung-Mahn Kim,* In-Hwan Park

Korea Research Institute of Chemical Technology, Yusong P. O. Box 107, Taejon 305-600, Korea
Fax +11(8)428614151; E-mail: kmkim@pado.krict.re.kr

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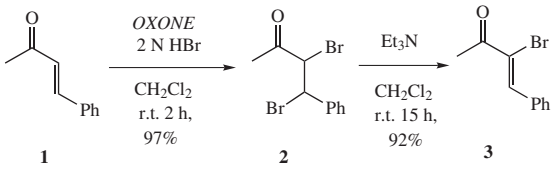
Abstract: Mixtures of *OXONE*® and hydrobromic acid or hydrochloric acid afford solutions of bromine or chlorine, respectively. α-Bromo- or α-chloro-α,β-unsaturated carbonyl compounds were prepared by addition of hydrobromic acid or hydrochloric acid to the mixture of α,β-unsaturated carbonyl compounds and *OXONE*® in CH_2Cl_2 followed by treatment of Et_3N in moderate to good yields.

Key words: halogenation, *OXONE*®, hydrobromic acid, hydrochloric acid, α,β-unsaturated carbonyl compounds

α-Halo-α,β-unsaturated carbonyl compounds are a class of important intermediates for the synthesis of α-carbon substituted enones[1] and natural products.[2] They are generally prepared by direct addition-elimination reaction with halogen (Br_2, Cl_2).[3] The use of molecular halogen suffers from potentially environmental hazard and the utilization in large scale operation often causes problem. Several indirect methods for the preparation of α-halo-α,β-enones have been studied such as addition-elimination of expensive phenylselenenyl halides,[4] deoxygenation of α,β-epoxy ketones with $BF_3{\cdot}Et_2O$ and tetraethylammonium bromide,[5] and the reaction of secondary alkynols with *N*-halosuccinimide in the presence of Koser's reagent[6] have been reported. Oxidative halogenation includes the reaction with HBr and hydrogen peroxide promoted by phase transfer catalyst,[7] with *OXONE*® and sodium halides,[8] with 1,1,1-triacetoxy-1,1-dihydro-1,2-benzidoxol-3(1*H*)-one (DMP) and tetraethylammonium bromide,[9] and with anhydrous HCl in DMF and mCPBA.[10] For recycling industrial by-product HCl or HBr, we have studied the oxidative halogenation of α,β-unsaturated carbonyl compounds and alkenes with hydrohalic acid (HBr and HCl) and *OXONE*® which is cost-effectiveness, efficient and mild oxidant with stable and nontoxic nature.

In continuation of our studies,[10a] we have examined the bromination of *trans*-4-phenyl-3-buten-2-one (**1**) with hydrogen bromide (30% in HOAc) in DMF and *OXONE*®, and found that the product was 3,4-dibromo-4-phenyl-2-butanone (**2**) in 67% yield. When the reaction with hydrogen bromide in DMF was replaced by hydrobromic acid (48% in water) in DMF with *OXONE*®, the isolated yield of dibromo-adduct (**2**) increased to 83%. When the same reaction was repeated with aqueous 2 N HBr (2 equiv) in CH_2Cl_2 enough to dissolve *OXONE*®, the 97% yield of **2** was achieved (Scheme 1). The results showed that molecular bromine is effectively generated by oxidation of hydrobromic acid with *OXONE*® in aqueous medium. In the reaction it was found to be easy to control the amount of bromine generated by adjusting concentration of hydrobromic acid with *OXONE*®.



Scheme 1

When the chlorination of **1** with 2 N HCl and *OXONE*® in CH_2Cl_2 was attempted, the product was the corresponding 3,4-dichloro-4-phenyl-2-butanone which was difficult to isolate due to its spontaneous dehydrochlorination during the purification procedure or upon standing neat at room temperature to afford stable 3-chloro-4-phenyl-3-buten-2-one.[8,10a] In an effort to optimize the yields of the halogen addition product, dehydrochlorination was conducted by cautious addition of Et_3N to afford 3-chloro-4-phenyl-3-buten-2-one (**3b**) in 77% of yield (*E*/*Z* ratio is 37:63). Similarly, treatment of 2 N HBr to a mixture of 4-phenyl-3-buten-2-one and *OXONE*® in CH_2Cl_2 followed by dehydrobromination with excess use of Et_3N afforded (*E*)-3-bromo-4-phenyl-3-buten-2-one (**3a**, 15%) and (*Z*)-3-bromo-4-phenyl-3-buten-2-one (**3a**, 77%), respectively (Table 1, entry 1). The structures of steroisomers are supported by the appearance of singlet vinylic proton in its NMR spectrum at δ = 7.37 (*E*-form) and δ = 8.03 (*Z*-form).[3a] The reaction of *trans*-cinnamaldehyde under the same condition was stereoselective and afforded exclusively *Z*-isomers of *trans*-2-bromo- or *trans*-2-chloro-cinnamaldehyde (**3c** and **3d**) in modest yields (entry 2). The bromination of sterically hindered 4-methyl-3-penten-2-one under the same condition gave excellent yield of dibromo adduct (isolated in 99% yield), but dehydrobromination with Et_3N was inefficient giving only 37% yield of 3-bromo-4-methyl-3-penten-2-one (**3e**, entry 3).

In a similar manner, treatment of other acyclic or cyclic enones such as n-4-hexen-3-one, 2-cyclohexenone and 4,4-dimethyl-2-cyclohexenone gave the corresponding α-halo enones in modest to good yields (entries 4–6). The

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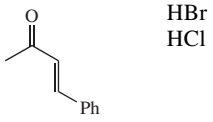
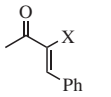
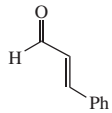
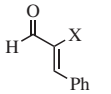
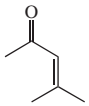
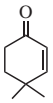
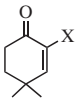
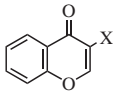
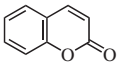
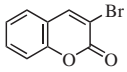
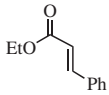
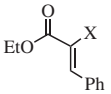
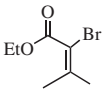
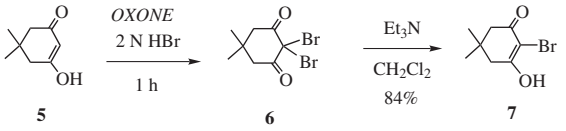
Table 1 Halogenation of α,β-Unsaturated Carbonyl Compounds Using *OXONE*® and Hydrobromic Acid or Hydrochloric Acid[a]

Entry	Substrate	HX	Product (X = Br, Cl)	Yield (%)[b] (*E*/*Z* ratios)[c]
1		HBr HCl		**3a** (92) (16:84)[d] **3b** (77) (37:63)[d]
2		HBr HCl		**3c** (70) (0:100)[d] **3d** (64) (0:100)[d]
3		HBr		**3e** (37)
4		HBr HCl		**3f** (74) **3g** (48)
5		HBr HCl		**3h** (99) **3i** (63)
6		HBr HCl		**3j** (98) **3k** (61)
7		HBr HCl		**3l** (55) **3m** (20)
8		HBr		**3n** (92)
9		HBr HCl		**3o** (89) (46:54) **3p** (82) (27:73)
10		HBr		**3q** (79)

[a] Substrate (5 mmol), *OXONE*® (3.7 g, 6 mmol) in CH_2Cl_2 (20 mL) and 2 N HX (X = Br or Cl, 11 mmol) were allowed to react for 2 h and Et_3N (3 equiv) was stirred for 2 h for dehydrohalogenation.
[b] Isolated yield determined by silica gel (70–230 mesh) column chromatography. All compounds showed satisfactory spectroscopic data (NMR, IR, Mass).
[c] The values in parenthesis are isolated yields of the stereoisomers.
[d] The ratios of stereoisomers were determined by ^1H NMR analysis.

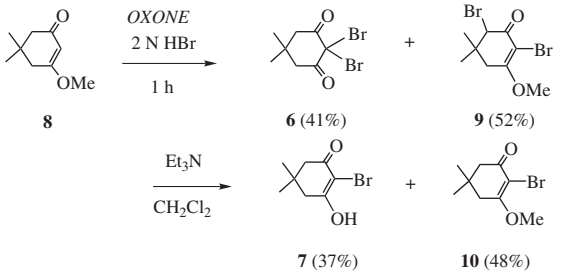
reaction with chromone gave low yields of α-chloro- and α-bromo-chromone in 20% and 55% yields, respectively, together with the recovered chromone (entry 7), whereas the reaction with coumarin, a class of cyclic lactone, gave excellent yield of α-bromo compound **3n** even in the reaction condition of 2 N HBr and *OXONE*® in DMF system (entry 8).

The strongly acidic condition may provide advantage for the halogenation of α,β-unsaturated esters, which does not work for NaBr or NaCl with *OXONE*® in two phase organic solvent and water.[7] Thus, the treatment of 2 N HBr or 2 N HCl with a mixture of ethyl *trans*-cinnamate and *OXONE*® in CH_2Cl_2 followed by dehydrohalogenation yielded the desired ethyl α-bromocinnamate (**3o**) or ethyl α-chlorocinnamate (**3p**) were obtained as a mixture of stereoisomers in good yields (entry 9). Similarly, when the reaction was repeated with sterically hindered ethyl 3,3-dimethacrylate under the same conditions, ethyl 2-bromo-3,3-dimethacrylate (**3q**) was isolated in 79% yield (entry 10).



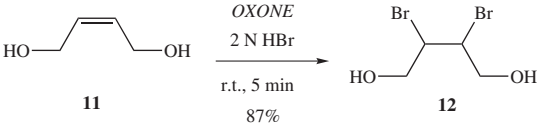
Scheme 2

The reaction of 5,5-dimethyl-3-hydroxy-cyclohex-2-enone (**5**) with 2 N HBr and *OXONE*® gave exclusively 2,2-dibromo compound **6** which was treated with Et_3N without isolation to afford 2-bromo-5,5-dimethyl-3-hydroxycyclohex-2-enone (**7**) in 84% yield (Scheme 2). On the other hand, the reaction of 5,5-dimethyl-3-methoxy cyclohexen-2-one (**8**) with 2 N HBr and *OXONE*® gave mixtures of 2,2-dibromo compound **6** and 2,6-dibromo compound **9**, which were treated with Et_3N to afford compound **7** and 2-bromo-5,5-dimethyl-3-methoxycyclohexen-2-one (**10**) in 37% and 48% yields, respectively (Scheme 3).[11]



Scheme 3

Similarly, the reaction proved to be effective in alkenes. The reaction of 1,4-dihydroxy-2-butene (**11**) and 2 N HBr in the presence of *OXONE*® afforded 2,3-dibromo-1,4-dihydroxybutane (**12**) in 87% yield in 5 minutes (Equation 1). Thus, the method appears to be quite general for α-halo-α,β-unsaturated carbonyl compounds and alkenes.



Equation 1

3-Bromo-4-phenyl-3-buten-2-one; General Procedure
To a mixture of 4-phenyl-3-buten-2-one (0.73 g, 5 mmol) and *OXONE*® (3.7 g, 6 mmol) in CH_2Cl_2 (20 mL) was added 2 N HBr (5.5 mL, 11 mmol of HBr) in one portion resulting in dark red colored solution. After stirring for 2 h at r.t., the color disappeared and Et_3N (4 mL) was added cautiously. After stirring for further 12 h and usual work-up, purification of the crude product by silica gel column chromatography afforded (*E*)-3-bromo-4-phenyl-3-buten-2-one (0.17g, 15%) and (*Z*)-3-bromo-4-phenyl-3-buten-2-one (0.86 g, 77%) as oil.

(*E*)-3-Bromo-4-phenyl-3-buten-2-one (3a)
IR (NaCl): 2347 (s), 1726 (m), 1710 (s), 1668 (s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.27 (s, 3 H), 7.23–7.37 (m, 6 H).

MS (70 eV): *m*/*z* (%) = 226 (23) [M + 2], 224 (25) [M^+], 145 (73), 102, 43 (100).

(*Z*)-3-Bromo-4-phenyl-3-buten-2-one (3a)
IR (NaCl): 2347 (m), 1726 (m), 1630 (s), 1467 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.61 (s, 3 H), 7.41–7.46 (m, 3 H), 7.85–7.90 (m, 2 H), 8.03 (s, 1 H).

MS (70 eV): *m*/*z* (%) = 226 (15) [M + 2], 224 (16) [M^+], 145 (73), 102 (100).

3,4-Dibromo-4-phenyl-2-butanone (2)
^1H NMR ($CDCl_3$): δ = 2.45 (s, 3 H), 4.93 (d, *J* = 11.8 Hz, 1 H), 5.32 (d, *J* = 11.8 Hz, 1 H), 7.37–7.43 (m, 5 H).

MS (70 eV): *m*/*z* (%) = 306 (5) [M + 2], 304 (15) [M], 302 (5) [M – 2], 225 (85).

(*E*)-3-Chloro-4-phenyl-3-buten-2-one (3b)
^1H NMR ($CDCl_3$): δ = 2.27 (s, 3 H), 7.17 (s, 1 H), 7.26–7.53 (m, 5 H).

MS (70 eV): *m*/*z* (%) = 180 (15) [M^+], 84 (100).

(*Z*)-3-Chloro-4-phenyl-3-buten-2-one (3b)
^1H NMR ($CDCl_3$): δ = 2.50 (s, 3 H), 7.25–7.41 (m, 3 H), 7.72 (s, 1 H), 7.81–7.85 (m, 2 H).

(*Z*)-2-Bromo-3-phenylpropanal (3c)
IR (KBr): 2348 (s), 1725 (m), 1669 (s), 1530 (s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.45–7.52 (m, 3 H), 7.90 (s, 1 H), 7.97–8.02 (m, 2 H), 9.34 (s, 1 H).

MS (70 eV): *m*/*z* (%) = 212 (47) [M + 2], 210 (49) [M^+], 103 (100), 102 (91).

(*Z*)-2-Chloro-3-phenylpropanal (3d)
IR (KBr): 2348 (s), 1694 (s), 1609 (s), 1121 (s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.45–7.53 (m, 3 H), 7.55 (s, 1 H), 7.91–7.98 (m, 2 H), 9.51 (s, 1 H).

MS (70 eV): *m*/*z* (%) = 167 (39) [M^+], 165 (100), 103 (89), 102 (55).

3-Bromo-4-methyl-3-penten-2-one (3e)
^1H NMR ($CDCl_3$): δ = 2.02 (s, 3 H), 2.03 (s, 3 H), 2.47 (s, 3 H).

4-Bromo-hex-4-en-3-one (3f)
IR (NaCl): 1693 (s), 1597 (m), 1619 (w), 1323 (m), 1188(m), 1158 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.14 (t, 3 H), 2.00 (d, *J* = 6.8 Hz, 3 H), 2.79 (q, 2 H), 7.25 (q, *J* = 6.8 Hz, 1 H).

MS (70 eV): *m*/*z* (%) = 178 (22.5) [M^+], 121 (22.8), 84 (46), 58 (58.6), 43 (100).

4-Chloro-hex-4-en-3-one (3g)
^1H NMR ($CDCl_3$): δ = 1.13 (t, 3 H), 1.98 (d, *J* = 6.8 Hz, 3 H), 2.76 (q, 2 H), 7.05 (q, *J* = 6.8 Hz, 1 H).

2-Bromocyclohex-2-en-1-one (3h)
IR (KBr): 1681 (s), 1652 (s), 1598 (s), 1318 (m), 1425 (m), 1125 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.02–2.15 (m, 2 H), 2.44–2.49 (m, 2 H), 2.52–2.67 (m, 2 H), 7.45 (t, *J* = 4.5 Hz, 1 H).

MS (70 ev): *m*/*z* (%) = 176 (24) [M + 2], 174 (23) [M^+], 148 (26), 146 (26), 86 (64), 84 (100).

2-Bromo-4,4-dimethylcyclohexeneone (3j)
IR (NaCl): 1697 (s), 1597 (m), 1468 (w), 1323 (m), 1145 (m), 813 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.17 (s, 6 H), 1.87 (t, *J* = 6.8 Hz, 2 H), 2.60 (t, *J* = 6.8 Hz, 2 H), 7.08 (s, 1 H).

MS (70 ev): *m*/*z* (%) = 205 (3.82) [M + 2], 203 (3.76) [M^+], 123 (100).

2-Bromochromone (3l)
Mp 94–98 °C.

IR (KBr): 1624 (s), 1529 (m), 1482 (m), 1089 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.24–7.49 (m, 2 H), 7.66–7.75 (m, 1 H), 8.22 (s, 1 H), 8.22–8.29 (m, 1 H).

MS (70 eV): *m*/*z* (%) = 226 (20) [M^+], 224 (24) [M], 145(13), 120 (38), 63 (100).

2-Bromocoumarine (3n)
Mp 110–111 °C.

^1H NMR ($CDCl_3$): δ = 7.28–7.35 (m, 2 H), 7.46–7.62 (m, 2 H), 8.11 (s, 1 H).

MS (70 eV): *m*/*z* (%) = 226 (73) [M + 2], 224 (73) [M + 2], 198 (21), 196 (21), 145 (27).

Ethyl α-Bromocinnamate (3o)
IR (NaCl): 1763 (s), 1636 (m), 1482 (m), 1247 (s), 1064 (s) cm^{-1}.

(*E*)-Ethyl α-Bromocinnamate: ^1H NMR ($CDCl_3$): δ = 1.18 (t, 3 H), 4.21 (q, 2 H), 7.26–7.36 (m, 6 H).

(*Z*)-Ethyl α-Bromocinnamate: ^1H NMR ($CDCl_3$): δ = 1.39 (t, 3 H), 4.36 (q, 2 H), 7.39–7.45 (m, 3 H), 7.83–7.88 (m, 2 H), 8.22 (s, 1 H).

MS (70 eV): *m*/*z* = 256 (24) [M + 2], 254 (25) [M^+], 175 (84), 147(100), 129 (33), 102 (81).

(*E*)-Ethyl α-Chlorocinnamate (3p)
^1H NMR ($CDCl_3$): δ = 1.17 (t, 3 H), 4.21 (q, 2 H), 7.25–7.36 (m, 6 H).

(*Z*)-Ethyl α-Chlorocinnamate (3p)
IR (NaCl): 1728 (s), 1618 (m), 1492 (m), 1263 (s), 1199 (s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38(t, 3 H), 4.36 (q, 2 H), 7.39–7.45 (m, 3 H), 7.82–7.87 (m, 2 H), 7.91 (s, 1 H).

MS (70 eV): *m*/*z* = 245 (7) [M^+], 244 (8), 210 (59), 147 (55), 129 (21), 102 (100).

Ethyl 2-Bromo-3,3-dimethylacrylate (3q)
IR (NaCl): 1728 (s), 1464 (m), 1371 (m), 1266 (s), 1182 (s), 1030 (m) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (t, 3 H), 1.92 (s, 3 H), 2.03 (s, 3 H), 4.39 (q, 2 H).

MS (70 ev): *m*/z (%) = 209 (16) [M + 2], 207 (18) [M$^+$], 135 (14), 55 (100).

2,2-Dibromo-5,5-dimethylcyclohexane-1,3-dione (6)
^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 6 H), 3.01 (s, 4 H).

MS (70 eV): *m*/*z* (%) = 300 (2.42) [M + 2], 298 (2.77) [M$^+$], 83 (100).

2-Bromo-5,5-dimethyl-3-hydroxycyclohex-2-en-1-one (7)
Mp 158–163 °C.

IR (KBr): 2347 (s), 1629 (s), 1529 (m), 1319 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.12 (s, 6 H), 2.44 (s, 2 H), 2.53 (s, 2 H), 6.61 (s, 1 H).

MS (70 eV): *m*/*z* (%) = 220 (19) [M + 2], 218 (20) [M$^+$], 164 (70), 162 (61), 83 (66), 55 (100).

2,6-dibromo-5,5-dimethyl-3-methoxycyclohex-2-en-1-one (9)
^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 3 H), 1.32 (s, 3 H), 2.41 (dd, *J* = 1.7 Hz, *J* = 16.8 Hz, 1 H), 2.45 (dd, *J* = 1.7 Hz, *J* = 16.8 Hz, 1 H), 4.11 (s, 3 H), 4.61 (d, *J* = 1.7 Hz, 1 H).

MS (70 eV): *m*/*z* (%) = 314 (11.81) [M + 2], 312 (11.87) [M$^+$], 124 (100).

2-Bromo-5,5-dimethyl-3-methoxycyclohex-2-en-1-one (10)
Mp 95–102 °C.

IR (KBr): 2347 (s), 1690 (s), 1610 (s), 1482 (m), 1385 (m), 1328 (m), 1269 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.13 (s, 6 H), 2.42 (s, 2 H), 2.54 (s, 2 H), 3.94 (s, 3 H).

MS (70 eV): *m*/*z* (%) = 234 (17.03) [M + 2], 232 (18.87) [M$^+$], 178 (22.29), 175 (29.67), 68 (91), 67 (100).

References

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