Pergamon

*Tetrahedron Letters*, Vol. 37, No. 14, pp. 2377-2380, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00295-X

# Oxidation of α,β-Enones and Alkenes with Oxone and Sodium Halides: A Convenient Laboratory Preparation of Chlorine and Bromine

R. Karl Dieter*, Lois E. Nice, and Sadanandan E. Velu

Hunter Laboratory, Department of Chemistry, Clemson University, Clemson SC 29634-1905.

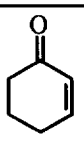
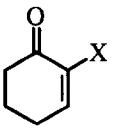
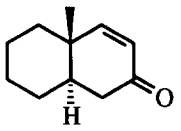
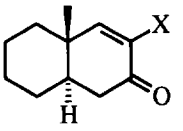
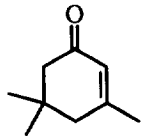
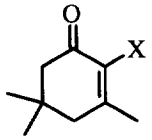
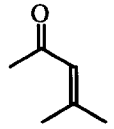
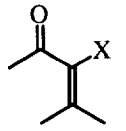
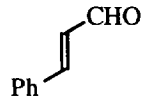
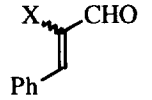
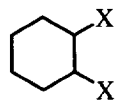
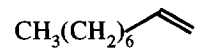
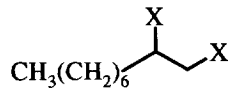
**Abstract**: Mixtures of oxone and sodium chloride or sodium bromide afford solutions of chlorine or bromine, respectively. These solutions effectively add chlorine and bromine to α,β-enones and alkenes. The method affords improved yields of 3-alkyl-2-halo-2-cycloalkenones which are sometimes difficult to prepare. Copyright © 1996 Elsevier Science Ltd

The addition of bromine across the double bond of α,β-enones[1] can be problematic depending upon substitution patterns. Several groups have reported that 3-alkyl-2-cycloalkenones gave poor yields of cyclic 2-bromoenones upon treatment with bromine in chlorinated hydrocarbon solvents followed by dehydrobromination.[2,3] The use of pyridinium bromide perbromide[3] in methylene chloride affords modest yields of 3-alkyl-2-bromocyclopentenones which have also been prepared from α,β-epoxy ketones[4] with $BF_3{\cdot}Et_2O$ and tetraethylammonium bromide. The addition of chlorine across α,β-enones has been less frequently utilized, perhaps reflecting the lack of a convenient laboratory source of chlorine. The addition of chlorine across simple unconjugated double bonds has been achieved with $HCl/H_2O_2$[5], $TeCl_4$/*tert*-BuOOH[6], and Amberlyst A-26($ICl_2^-$).[7] Bromine has been generated *in situ* by electrolysis in a strongly acidic medium.[8] Mechanistic pathways for halogenation of enones under acidic conditions and under conditions involving acid scavengers have been proposed but not fully elucidated.[9]

We have discovered that aqueous mixtures of oxone ($2\ KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) and sodium chloride or sodium bromide rapidly generate chlorine and bromine, respectively, and that these strongly acidic solutions may confer some advantage in the addition of halogens to α,β–enones. In an initial investigation, a two phase organic solvent/brine solution containing cyclohexenone was treated with oxone. The reaction mixture gave 2,3-dichlorocyclohexanone which underwent dehydrohalogenation upon standing neat at room temperature. In an effort to optimize the yields of the chlorine addition product, the initial adduct was treated with $Et_3N$ to afford the stable and easily purified 2-chloro-2-cyclohexenone (**1**, X = Cl). Examination of various reaction conditions, revealed that comparable yields of **1** (X = Cl) could be obtained with homogenous solutions formed with acetone or ethyl acetate (Table, entries 1-2) or two phase solvent systems using pentane or $CCl_4$ (entries, 3-4) although the pentane system gave the lowest yield. NMR evidence suggested that the use of acetone or ethyl acetate resulted in α-chlorination of these solvents to afford minor by-products. The reaction did not work in water alone (entry 5) or in the absence of water obtained by adding oxone and solid NaCl to an organic solvent. Slightly better yields of **1** could be obtained by first generating chlorine and then adding cyclohexenone to the two phase system (entry 6).

Similarly, treatment of a $CCl_4$/aqueous NaBr/cyclohexenone mixture with oxone followed by dehydrobromination with $Et_3N$ gave the desired 2-bromo-2-cyclohexenone in modest yield. The reaction was

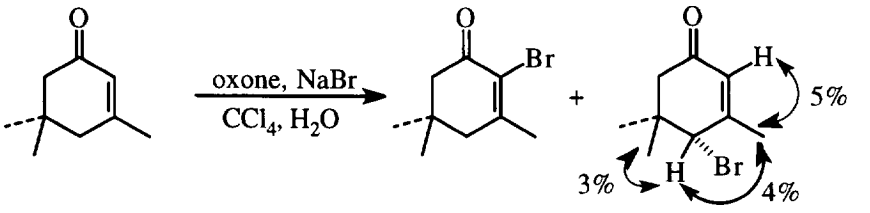
Table. Addition of Oxone generated chlorine and bromine to enones and alkenes.

| entry | substrate | NaX | solvent[a] | temp(°C) | method[c] | product (X=Cl, Br) | % yield[d] |
|---|---|---|---|---|---|---|---|
| 1 |  | Cl | acetone/$H_2O$ | >25 | A |  | 70 |
| 2 | | Cl | EtOAc /$H_2O$ | >25 | A | | 72 |
| 3 | | Cl | pentane/$H_2O$ | >25 | A | | 51 |
| 4 | | Cl | $CCl_4$ / $H_2O$ | >25 | A | | 66 |
| 5 | | Cl | $H_2O$ | >25 | A | | - |
| 6 | | Cl | $CCl_4$ / $H_2O$ | 0 | B | | 87 |
| 7 | | Br | $CCl_4$ / $H_2O$ | 0 | B | **1** | 82 |
| 8 |  | Cl | acetone/H20 | >25 | A |  | 64 |
| 9 | | Br | $CCl_4$ / $H_2O$ | 0 | B | | 56 |
| | | | | | | **2** | |
| 10 |  | Cl | $CCl_4$ / $H_2O$ | 0 | A |  | 87 |
| 11 | | Cl | | 0-25 | B | | 100 |
| 12 | | Br | | >25 | A | | 74 |
| 13 | | Br | | 40 | B | **3** | 90 [e] |
| 14 |  | Cl | $CH_2Cl_2$ [f] | 25 | - |  | 71 |
| 15 | | Br | $CCl_4$ / $H_2O$ | 0 | B | | 49 |
| | | | | | | **4** | |
| 16 |  | Cl | | 60 | A |  | 38 |
| 17 | | Br | | >25 | A | | 70g |
| | | | | | | **5** | |
| 18 |  | Cl | | 0 | A |  | 78 |
| 19 | | Br | | 0 | B | | 79 |
| | | | | | | **6** | |
| 20 |  | Cl | | 0 | B |  | 96[h] |
| 21 | | Br | | 0 | B | | 98[h] |
| | | | | | | **7** | |

[a] A 5:1 organic solvent/$H_2O$ ratio was used unless otherwise noted. [b] Method A resulted in an exothermic process that warmed the solution. [c] A = i. enone, NaX. ii. oxone. iii. $Et_3N$, $CH_2Cl_2$. B = i. oxone, NaX. ii. enone. iii. $Et_3N$, $CH_2Cl_2$. [d] Yields are based upon isolated products purified by column chromatography unless otherwise noted. [e] Mixture of 2-bromoisophorone (90%) and 4-bromoisophorone (6%). [f] Oxone generated chlorine gas passed through a dry $CH_2Cl_2$/enone solution. [g] Mixture of stereoisomers (44:26). [h] Yields based upon crude material >95% pure by NMR analysis.

cleaner and higher yielding when cyclohexenone was added after $Br_2$ formation (**1** X = Br, entry 7). These procedures could be readily extended to a bicyclic enone affording **2** in modest yields (entries 8-9).

The addition of chlorine to isophorone, a β-alkyl substituted cyclic enone proved uneventful, although significantly better yields of the 2-chloro-2-enone (**3** X = Cl) could be obtained by addition of the enone to preformed chlorine (entries 10 vs 11). The attempted bromination of isophorone proved to be much more problematic. Initial addition of oxone to a isophorone/$CCl_4$/aq NaBr solution gave a 60:40 mixture of the 2-bromo[3] and 4-bromo enone[10] (eq. 1). The 2-bromoenone structure could be easily identified from $^1H$ and $^{13}C$ NMR data while assignment of the 4-bromo product rests upon NOE experiments. Irradiation of the bromomethine proton induces an enhancement in the absorption intensity of both geminal methyls and more significantly of the 3-methyl substituent. The ratio of products obtained upon addition of isophorone to preformed $Br_2$ was temperature dependent; the 4-bromo product predominating at low temperatures and the 2-bromo product predominating at higher temperatures. Between 30 and 40°C both procedures selectively gave the 2-bromo product in good yields.




eq. 1

| conditions | temp (°C) | % yield | |
|---|---|---|---|
| i. oxone, enone. ii. NaBr. | 25 | 60 | 40 |
| | 35 | 74 | 6 |
| i. oxone, NaBr. ii. enone. | 0 | | 45 |
| | 25 | 19 | 66 |
| | 40 | 90 | 6 |

The addition of *in situ* oxone generated chlorine to mesityl oxide or cinnamaldehyde in the $CCl_4/H_2O$ two phase solvent system proved to be problematic affording a complex mixture of products. Utilization of higher reaction temperatures, longer times, or sequence of oxone addition in the chlorination of mesityl oxide afforded complex reaction mixtures which appeared to contain polychlorinated products. Such an outcome would be consistent with the α-halogenation of ketones which are often achieved in polar solvents (e.g., $Br_2$/MeOH).[11] Alternatively, generation of chlorine in a separate flask and then bubbling the $Cl_2$ through a $CH_2Cl_2$ solution of mesityl oxide afforded, after dehydrohalogenation, **4** (X = Cl) in excellent yield (entry 14) without the formation of substantial polychlorinated products. Dehydrohalogenation of the dihalide to **4** (X = Cl) was inefficient with $Et_3N$ and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) gave higher yields. When the reaction was carried out in the presence of *p*-TsOH (10 mole %, dry $CH_2Cl_2$) the chlorination was incomplete yielding the vicinal dichloride and starting material (1:1.25). The addition of oxone generated bromine to mesityl oxide or cinnamaldehyde under the

$CCl_4/H_2O$ two phase system was less problematic and afforded the 2-bromoenone **4** (X = Br) and aldehyde **5** (X = Br, mixture of **E** and **Z** stereoisomers)[12] in modest to good yields (entries 15 & 17).

The halogenation of simple alkenes was briefly examined. Both cyclic and acyclic alkenes afforded excellent yields of the vicinal dihalo compounds upon treatment with *in situ* generated chlorine or bromine with oxone in a two phase solvent system (entries 18-21).

In summary, mixtures of oxone and NaCl or NaBr afford a convenient laboratory preparation of molecular chlorine or bromine, respectively, which can be used *in situ* for addition across both conjugated enones and enals, and simple alkenes. The procedure does not work for conjugated enoates. These reaction conditions provide a solution to the reported difficulties in the addition of bromine across 3-alkyl substituted cyclic enones and the efficacy of the procedure appears to be a result of the acidic nature of the reaction medium. It is intriquing that in these two phase solvent systems ($CCl_4/H_2O$) cleaner reactions and higher yields of 2,3-dihaloketones are obtained while removal of acid is beneficial in chlorocarbon solvents.[3] Increased yields of dihaloketones from α,β-enones have previously been observed with acidic $CH_3OH/Br_2$ systems.[9] The regioselective bromination of isophorone is both intriquing from a mechanistic perspective and potentially synthetically useful.

**Acknowledgements**: We gratefully acknowledge the National Science Foundation for support of this work.

## References

1. (a) Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M. Korn, A. *Org. Syn.* **1983**, *61*, 65. (b) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.*, **1982**, *47*, 1855.
2. (a) Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.*, **1968**, *33*, 1454. (b) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.*, **1982**, *47*, 5088.
3. Dauben, W. G.; Warshawsky, A. M. *Synth. Commun.*, **1988**, *18*, 1323.
4. Mandal, A. K.; Mahajan, S. W. *Tetrahedron* , **1988**, *44*, 2293.
5. Olah, G. A.; Gupta, B. G. B.; Ho, T. L. *Synthesis*, **1977**, 676.
6. Uemura, S.; Fukuzawa, S. *J. Organomet. Chem.*, **1984**, *268*, 223.
7. Manescalchi, F.; Bongini, A.; Cainelli, G.; Contento, M. *J. C. S. Chem. Commun.*, **1980**, 1278.
8. Torii, S.; Uneyama, K.; Tanaka, H.; Yamanaka, T.; Yasuda, T.; Ono, M.; Kotmoto, Y. *J. Org. Chem.*, **1981**, *46*, 3312.
9. (a) Atkinson, R. C.; de la Mare, P. B. D.; Larson, D. S. *J. Chem. Soc. Perkin Trans. 2*, **1983**, 271. (b) Heasley, V. L.; Louie, T. J.; Luttrull, D. K.; Millar. M. D.; Moore, H. B.; Nogales, D. F.; Sauerbrey, A. M.; Shevel, A. B.; Shibuya, T. Y.; Stanley, M. S.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.*, **1988**, *53*, 2199. (c) Heasley, V. L.; Elliott, S. L.; Erdman, P. E.; Figueroa, D. E.; Krosley, K. W.; Louie, T. J.; Moore, H. B.; Mudge, B. P.; Nogales, D. F.; Nordeen, J.; Oakes, M. L.; Rosbrugh, J. W., Jr.; Sauerbrey, A. M.; Shibuya, T. Y.; Stanley, M. S.; Stewart, C. C.; Shellhamer, D. F.; Heasley, G. E. *J. Chem. Soc. Perkin Trans. 2*, **1991**, 393.
10. Tsuboi, S.; Kurihara, Y.; Watanabe, T.; Takeda, A. *Synth. Commun.*, **1987**, *17*, 773.
11. Gaudry, M.; Marquet, A. *Org. Syn.*, **1976**, *55*, 24.
12. Kingsbury, C. A.; Draney, D.; Sopchick, A.; Rissler, W.; Durham, D. *J. Org. Chem.*, **1976**, *41*, 3863.

(*Received in USA* 31 *January* 1996; *accepted* 8 *February* 1996)