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Synthesis of α-Halomethyl Ketones: Oxidative Hydrolysis of Vinyl Halides

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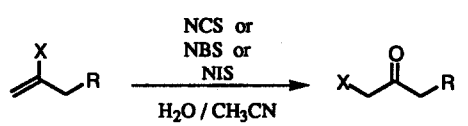
Abstract: Oxidative hydrolysis (e.g. aqueous NBS) of various vinyl halides affords the corresponding α-halomethyl ketones in good yield and purity.

α-Haloketones are useful synthetic intermediates, and numerous methods exist for their regiospecific formation.[1] They have been prepared by treating alkyl enol ethers, trimethylsilyl enol ethers, enol acetates and enamines with a variety of electrophilic halogenating agents.[2] However, the utilization of enol ethers is somewhat limited due to their overall chemical reactivity and poor hydrolytic stability.[3] Vinyl chlorides possess a higher degree of hydrolytic stability[4] and can be transformed to α-chloroketones utilizing a two step oxidation (*m*-chloroperbenzoic acid)-rearrangement procedure.[5] To the best of our knowledge, the application of the latter methodology to the preparation of α-bromo- and α-iodoketones has not been demonstrated. Recently, as part of our work in the preparation of N-(*tert*-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine, we reported the oxidative hydrolysis [aqueous N-bromosuccinimide (NBS)] of a vinyl bromide to an α-bromoketone.[6] Attracted by the simplicity of these reaction conditions, coupled with our interest in the synthesis of α-haloketones, we decided to investigate the oxidative hydrolysis of a variety of vinyl halides. Herein, we report on the successful utilization of this methodology for the general preparation of α-chloro-, α-bromo- and α-iodomethyl ketones (Scheme 1).[7]



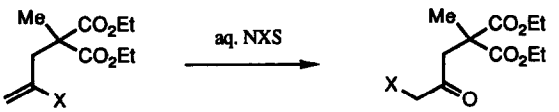
1 X = Cl, Br 2 X = Cl, Br, I

Scheme 1

Some of the results we have obtained are summarized in Table I. Under our experimental conditions, vinyl bromides (**1**, X=Br) are smoothly transformed into α-bromomethyl ketones. Thus, treatment of the vinyl bromides with NBS (1.1 - 1.5 equivalents) in aqueous acetonitrile (CH_3CN / H_2O, 4:1) containing a catalytic amount of HBr gave the desired α-bromoketones in good yield (Table I, entries 1-7, 9-11). None of the corresponding regioisomeric α-bromoketones were observed. In most cases, small amounts (5 to 15 %) of

unidentified di- and tribrominated side products were also formed, and these were easily removed by chromatography.[8,9] Upon the addition of NBS, a yellow color immediately developed indicating the in situ generation of a bromine - hypobromous acid equilibrium. The hypobromous acid thus produced is most likely responsible for the oxidative hydrolysis of the vinyl bromide moiety.[10] In the absence of HBr, a variable induction period was noted.[11] Bromine could also be used for this transformation (Table I, entry 8). The chemoselective transformation of the vinyl bromides **7** and **21** underscores the utility of this method. Formation of the bromoketone **27** should find utility in the synthesis of unnatural amino acids (Table I, entry 14).[12] It should be noted that esters, amides, ketones, acetates and tosylates appear to be stable to the oxidative hydrolysis reaction. However, acid labile protecting groups such as MEM ethers and *tert*-butyldiphenylsilyl ethers were cleaved under these reaction conditions.[13] Interestingly, substrates which lacked an oxygenated functionality in proximity to the vinyl halide moiety gave poorer yields of the desired α-bromoketones (Table I, entry 11 vs. 12, 13, and 15).[14]

This reaction is also applicable to the formation of α-chloro and α-iodomethyl ketones (Scheme 2). Treatment of the vinyl chloride **30** with N-chlorosuccinimide (1.3 equiv. NCS, CH_3CN / H_2O 4:1, cat. HCl) resulted in the smooth formation (6h, rt.) of the α-chloroketone **31** in 86 % yield. Similarly, treatment of **30** with 1.3 equiv. of NBS or N-iodosuccinimide (NIS) afforded the corresponding α-bromoketone **16** and α-iodoketone **32** in 84% and 82% yield, respectively. The latter products contained small amounts (5-10%) of the chloroketone **31**.[15] Thus, through the appropriate choice of the halogenating agent, one substrate can provide a variety of α-haloketones.[16] Surprisingly, treatment of the vinyl bromide **15** with NCS resulted in almost exclusive formation of the α-bromoketone **16**.



Scheme 2

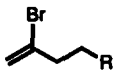
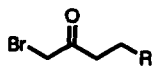
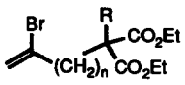
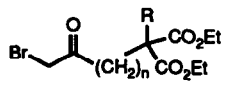
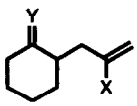
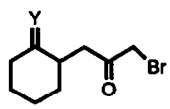
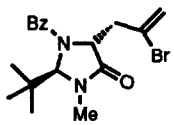
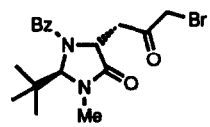
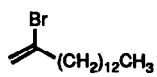
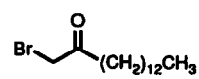
30 X = Cl
15 X = Br

31 X = Cl
32 X = I
16 X = Br

In summary, the oxidative hydrolysis of vinyl halides can be used for the regioselective synthesis of α-chloro-, α-bromo- and α-iodomethyl ketones. The demonstrated potential of this approach, coupled with the availability[17] and hydrolytic stability of vinyl halides, offers considerable advantages over existing methodologies. The synthetic utility of this procedure is under further investigation.[18]

The following procedure is representative. To a stirred solution of the vinyl bromide **15** (293 mg, 1 mmol.) in an acetonitrile (8 mL)-water (2 mL) mixture was added NBS in one portion. A catalytic amount of conc. HBr (48% , 2 μL) was then added. The resultant yellow solution was stirred at room temperature for 3h. The reaction mixture was then diluted with diether (30 mL) and treated dropwise with aqueous sodium thiosulfate (5% w/v) until the yellow color had disappeared. The mixture was then transferred to a separatory funnel, and the organic layer washed with aqueous $NaHCO_3$ (5% w/v, 2 x 5 mL) and saturated brine. Drying ($MgSO_4$) gave, after filtration and concentration, the crude reaction product, which was purified by flash chromatography on silica gel to afford 266 mg (86%) of the desired α-bromomethyl ketone **16** as an oil.[9]

Table I: Preparation of α-Bromomethyl Ketones[a]

Entry	Vinyl Bromide	α-Bromomethyl Ketone	Yield[b] (%)
			
1	**3** R= CO_2Et	**4** R= CO_2Et	81
2	**5** R= $C(O)NEt_2$	**6** R= $C(O)NEt_2$	60[c]
3	**7** R= $C(O)CH_3$	**8** R= $C(O)CH_3$	85
4	**9** R= CH_2OAc	**10** R= CH_2OAc	82
5	**11** R= CH_2OTs	**12** R= CH_2OTs	76
			
6	**13** n =1, R= H	**14** n = 1, R= H	63[d]
7	**15** n =1, R= CH_3	**16** n =1, R= CH_3	86
8	**15** n =1, R= CH_3	**16** n =1, R= CH_3	82[e]
9	**17** n =3, R= CH_3	**18** n =3, R= CH_3	71
10	**19** n = 1, R = HNAc	**20** n = 1, R = HNAc	85[f]
			
11	**21** Y = O, X = Br	**22** Y = O	85
12	**23** Y = H_2, X = Br	**24** Y = H_2	--[g]
13	**25** Y= H_2, X = Cl	**24** Y = H_2	52
14	 **26**	 **27**	77
15	 **28**	 **29**	59

a) Unless otherwise stated all reactions were carried out according to the representative procedure, see text. b) Isolated, purified product. c) >90% pure by GCMS. d) ~25% of 2-brominated material (13, R=Br) was also formed. e) 1.3 equiv. of bromine was used. f) From ref. 6. g) GCMS analysis showed < 30% of 24 in the crude reaction product.

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7. Since our earlier work (ref. 6) two other applications of this reaction have been reported. (a) Chung, J.Y.L.; Reamer, R.A.; Reider, P.J. *Tetrahedron Lett.* **1992**, *33*, 4717-4720. (b) Hutchinson, J.H.; McEachern, E. J.; Scheigetz, J. *Tetrahedron Lett.* **1992**, *33*, 4713-4716. The hypochlorous acid induced oxidative hydrolysis of vinyl chlorides is known, but it has not been recognized as a general route to haloketones, see: (c) Ballinger, P.; De La Marie, P.B.D.; Williams, D.L.H. *J. Chem. Soc.* **1960**, 2467-2472 and references cited therein.
8. In general, the formation of these side products (see ref. 7c) was reduced by using polar solvents (e.g. CH_3CN, N,N-dimethylformamide and ethanol). Tetrahydrofuran gave poor results. Easily brominated functionalities may also interfer, (e.g. Table 1, entry 7).
9. All starting materials and reaction products exhibited spectral data (NMR, IR, MS) in accordance with their assigned structures. Purified products were > 95% pure as judged by GCMS and NMR analysis.
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11. For an observation of a similar induction period in the formation of hypobromous acid, see ref. 10. The addition of HBr to NBS is known to liberate bromine which in an aqueous environment will form hypobromous acid, see: March, J. *Advanced Organic Chemistry, 3rd Edition*, John Wiley & Sons, 1985, page 625.
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13. In theory, 1 equiv. of HBr is formed as a reaction co-product. The addition of acid scavengers (e.g. BaO, 2,6-lutidine) retarded the reaction rate, and heating was required (40-50°C) to get a reasonable conversion of starting material. Nonetheless, MEM and silyl ethers were cleaved even under the latter reaction conditions.
14. A similar proximity effect has been noted in the HOBr addition to alkynes. Akhrem, A.A. *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* **1960**, 639-702.
15. In these reactions the amount of the chloroketone increased with prolonged reaction times. Thus, the latter could be minimized by immediately quenching the reaction upon complete consumption of the starting material. See also Table I, entry 13.
16. The use of the vinyl bromides and NBS (or bromine) is recommended when material free of the chloroketone is desired.
17. The majority of the vinyl halides use in this study were prepared by alkylation of the appropriate nucleophile (eg. NaH/diethyl methylmalonate, dodecylmagnesium iodide, etc.) with commercially available 2,3-dihalopropenes. Manipulation of the ester groups then provided the additional substrates listed in Table I. For other methods to prepare vinyl halides, see: Curran, D.P. *Synlett.* 1991, 63-72 and references cited therein.
18. Leanna, M.R.; Morton, H.E. the following communication in this issue.

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