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Graphical Abstract

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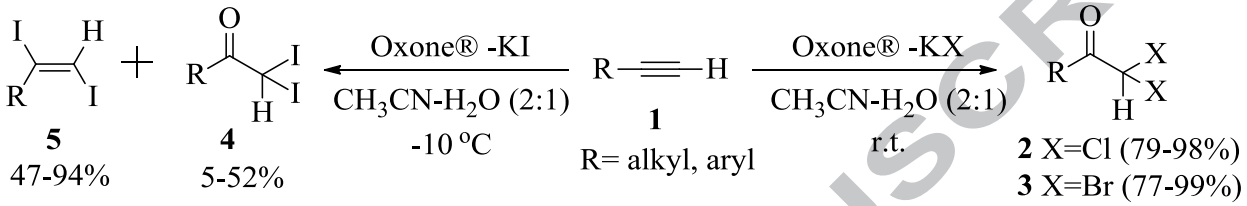

A new and efficient method for the synthesis of α,α-dihaloketones by oxyhalogenation of alkynes using Oxone®-KX (X=Cl, Br or I)

Sridhar Madabhushi,* Raveendra Jillella, Kishore Kumar Reddy Mallu, Kondal Reddy Godala and Venkata Sairam Vangipuram

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Abstract: A simple and efficient method for the preparation of α, α-dichloroketones, α, α-dibromoketones and α, α-diiodoketones by oxyhalogenation of alkynes using oxone® and KX(X =Cl, Br or I) is described.

Keywords: oxone®, potassium halide, oxyhalogenation, alkynes, α, α-dihaloketones.

α,α-Dihaloketones are important intermediates for synthesis of heterocycles,[1] unsaturated acids and ynols,[2] and also useful in cyclopropanation reactions.[3] These compounds are generally obtained in poor yields by halogenation of α-methyl ketones with bromine or chlorine.[4] In recent years, oxyhalogenation of alkynes has emerged as an important reaction for the preparation of α,α-dihaloketones. Shreeve *et al.*[5] have prepared α,α-dibromoketones by oxybromination of alkynes with KBr using Selectfluor® as an oxidant. In another study, Floris *et al.*[6] have achieved oxybromination of alkynes with KBr using hydrogen peroxide as an oxidant and $(NH_4)_2MoO_4$ as the catalyst. In this method, α,α-dibromoketones were formed in moderate yields along with a mixture of other products. Recently, Li and co-workers[7] studied oxyhalogenation of alkynes using *N*-halosuccinimide as the halogen source and $FeCl_3{\cdot}6H_2O$ as the oxidant. In this reaction, *N*-halosuccinimide is required in stoichiometric quantity and this gives mixtures, as succinimide is invariably produced as a byproduct. Recently, Itoh and co-workers[8] reported a photochemical approach for oxybromination by aerobic photooxidation of alkynes using 48% aqueous HBr and

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obtained α,α- dibromoketones in 17-84% yields. Most of the studies on oxyhalogenation of alkynes are limited to preparation of α,α-dibromoketones and they also suffer from one or more disadvantages such as poor yields, application of expensive or toxic chemicals and formation of mixture of products. Hence, studies for development of more convenient and efficient methods for oxyhalogenation of alkynes into α,α-dihaloketones are highly desirable.

Potassium peroxymonosulfate or oxone®, which is commercially available in the form of a triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, is an important and widely used oxidant in organic synthesis for a variety of transformations such as oxidation of alkenes to epoxides,[9] thioethers to sulfones,[10] aldehydes to carboxylic acids[11] and tertiary amines to amine oxides.[12] In addition, oxone® is also known to promote bromination,[13] hydroxybromination[14] and benzylic oxidation[15] reactions with reagents such as NH_4Br and KBr. To the best of our knowledge, studies on transformation of alkynes into α,α-dihaloketones using oxone® as the oxidant are so far not reported in literature. Herein, we report, a simple and efficient method for the preparation of a variety of α,α-dichloroketones (79-98%), α,α-dibromoketones (77-99%) and α,α-diiodoketones(5-52%)) by oxyhalogenation of alkynes with a potassium halide using oxone® as the oxidant as shown in Scheme 1.

Scheme 1: Oxyhalogenation of alkynes with oxone-KX

In our preliminary experiments, we examined the scope of oxone® mediated oxyhalogenation of an alkyne using phenylacetylene, which was reacted with a variety of halogen sources such as

aq. HCl, NH_4Cl, NaCl, KCl, aq. HBr, NH_4Br, KBr, KI, *N*-chlorosuccinimide in the presence of oxone® in acetonitrile- water and the results are shown in Table 1.

Table 1: A study of various halogen sources for conversion of phenyacetylene into α,α-dihaloacetophenone using oxone® as the oxidant.

In the above study, best results were observed with potassium halides. For example, the reaction with oxone®-KCl gave 2,2-dichloro-1-phenylethanone in 98% yield (entry 4, Table 1), reaction with oxone®-KBr gave 2,2-dibromo-1-phenylethanone in 99% yield (entry 7, Table 1) and the reaction with oxone® -KI gave 2,2-diiodo-1-phenylethanone in 52% yield (entry 10, Table 1). These oxyhalogenation reactions were found to proceed well in acetonitrile and water and no reaction was observed in the absence of water.

In our study, rapid exothermic reaction was observed when oxone® was mixed with KX (KCl, KBr or KI) in water. In our observation, α, α-dihaloketone formed in high yield under controlled reaction temperatures. For example, in the above study, we obtained 2,2-dichloro-1-phenylethanone and 2,2-dibromo-1-phenylethanone in good yields when reaction temperatures were kept below 50 ^{o}C. In oxyiodination reaction of phenylacetylene with oxone®-KI, we obtained 2,2-diiodo-1-phenylethanone in good yield when reaction temperature was maintained below -10 ^{o}C. In these reactions, exothermicity was conveniently controlled with slow (dropwise) addition of water to the reaction mixture, i.e., to the mixture of phenylacetylene, potassium halide and oxone® in acetonitrile, at room temperature.

Next, using the above optimized reaction procedures, we studied oxychlorination and oxybromination and oxyiodination reactions of a variety of alkynes **1a-j** with oxone®-KCl, oxone®-KBr and oxone®-KI respectively in acetonitrile and water.[16] In this study, oxychlorination and oxybromination of alkynes **1a-j** gave corresponding α,α-dichloroketones **2a-j** in 79-98% yields and α,α-dibromoketones **3a-j** in 77-99% yields respectively. However, in oxyiodination reactions of alkynes **1a-j**, we obtained mixtures of α,α-diiodoketones **4a-j** (5-52%) and 1,2-diiodo alkenes **5a-j** (47-94%) as shown in Table 2.

Table 2: Oxyhalogenation of alkynes using oxone® -KX

The plausible mechanism for the formation of α,α-dihaloketones by reaction of oxone®-KX system with an alkyne is shown in Scheme 2. Here, in the initial step, oxone® and KX react in water to give hypohalous acid (HOX).[17] Next, hypohalous acid converts into dihalo monoxide (X_2O)[18] and reacts with alkyne to give a cyclic alkyne-halonium ion complex, which collapses into more stable vinyl carbocation and undergoes nucleophilic addition reaction with XO^- producing α, α-dihaloketone as shown in Scheme 2. Here, the terminal alkyne undergoes nucleophilic(XO^-) addition reaction with Markovnikov's regiochemistry as 2^o vinyl carbocation is more stable than 1^o vinyl carbocation.[19] In this mechanism, alkyne-bromonium ion complex collapses to 2^o vinyl carbocation, which is being stabilized by the hyperconjucation or electron releasing inductive effect of the adjacent R group(alkyl or aryl).

Scheme 2: Plausible mechanism for conversion of an alkyne into a α, α-dihaloketone

In the present study, though we did not observe formation of 1,2-dichloroalkene and 1,2-dibromoalkene in oxychlorination and oxybromination reactions, we observed formation 1,2-diiodoalkene as a side product in oxyiodination reaction of an alkyne with oxone®-KI. Here, it appears that I_2O is less stable when compared to Cl_2O and Br_2O at temperatures below -10 ^oC. Thermal splitting of I_2O can generate iodine,[20] which readily reacts with an alkyne to give a 1,2-diiodoalkene.[21]

In conclusion, this work describes the first study of application of oxone® as an oxidant for oxyhalogenation of alkynes into α, α-dihaloketones. In this study, a simple and efficient method was shown for efficient conversion of a variety of alkynes into α, α-dichloroketones, α, α-dibromoketones and α, α-diiodoketones under mild conditions.

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Supplementary data: Supplementary data (experimental procedures, characterization data and ^1H &^{13}C NMR spectra of the compounds) associated with this article could be found in the support information.

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16. ***A typical procedure for preparation of α,α-dichlorketons and α,α-dibromoketones***: 1-Ethynyl-4-methylbenzene **1b** (0.5 g, 4.3 mmol), KBr (1.0 g, 8.6 mmol), oxone® (5.3 g, 8.6 mmol) and acetonitrile (10 mL) were taken into a 100 mL round bottomed flask and stirred at room temperature. Next, water (5 mL) was added dropwise to the mixture. With addition of water, exothermic reaction was observed and temperature of the reaction mixture increased to 50 ^{o}C. After completion of the reaction (TLC), reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by normal column chromatography (silica gel 60-120 mesh, *n*-hexane) furnished 2,2-dibromo-1-*p*-tolylethanone **3b** (1.22 g, 97%) as a pale yellow solid (m.p. 96-98 ^{o}C; lit.[22] 97-99 ^{o}C), which was characterized by the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.69 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.5, 145.6, 129.7, 129.5, 128.0, 39.9, 21.7; IR (neat): υ 3012, 2932, 1708, 1423, 1282, 993, 748, 682 cm^{-1}; Elemental Analysis: C, 37.14; H, 2.775%; Calcd: C, 37.04; H, 2.76%;

A typical procedure for preparation of α,α-diiodoketones: 1-Ethynyl-4-methylbenzene **1b** (0.5 g, 4.3 mmol), KI (1.4 g, 8.6 mmol), oxone® (5.3 g, 8.6 mmol) and acetonitrile (10 mL)

were taken into a 100 mL round bottomed flask and the mixture was cooled to -10 ^{o}C using a salt-ice bath. Next, water (5 mL) was added drop wise to the mixture and after completion of the reaction (TLC), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3x15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by normal column chromatography (silica gel 60-120 mesh, *n*-hexane) furnished 2,2-diiodo-1-*p*-tolylethanone **4b** (0.86 g, 52%) as a pale yellow solid (m.p. 75-77 ^{o}C) and (*E*)-(1,2-diiodovinyl)benzene **5b** (0.76 g, 47%) as a pale yellow oil. Spectral data obtained for **4b** and **5b** are as follows:

***2,2-diiodo-1-p-tolylethanone*(4b):** pale yellow solid, m.p. 75-77 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 6.50 (s,1H), 2.44 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.8, 145.3, 129.5, 129.6, 125.8, 21.7, -28.2; IR (KBr): υ 3036, 2925, 1718, 1456, 1262, 968, 801 cm^{-1}.

***(E)-1-(1,2-diiodovinyl)-4-methylbenzene*(5b):** yellow oil, ^{1}H NMR ($CDCl_3$ 300 MHz,): δ= 7.25(d, J = 8.1 Hz, 2H), 7.20(s, 1H), 7.15(d, J = 7.9 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 131.0, 129.9, 115.3, 99.4, 81.7, 20.5; IR (neat): υ 3063, 3012, 2948, 2851, 1416, 1201, 1152, 989, 789 cm^{-1}.

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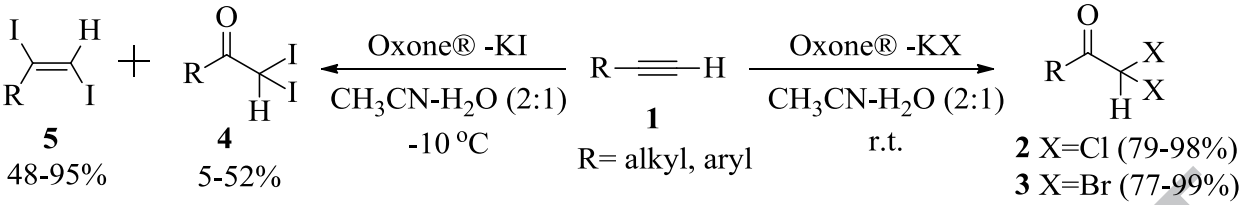
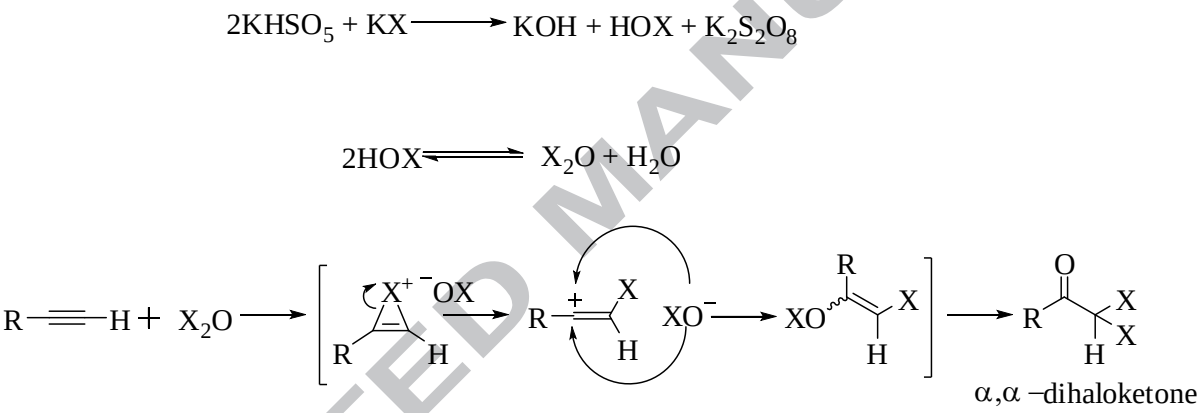
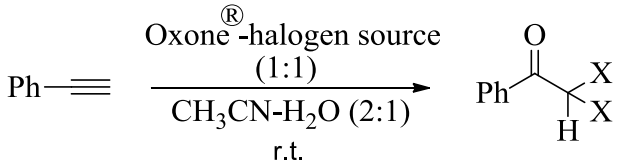


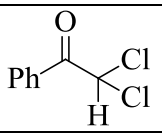
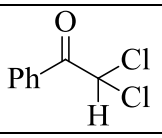
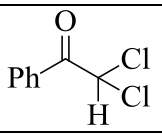
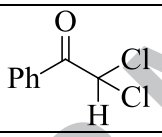
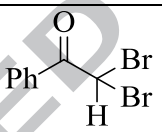
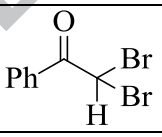
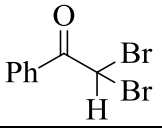
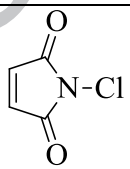
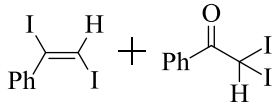
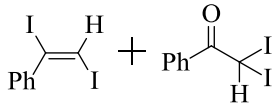
Scheme 1: Oxyhalogenation of alkynes with Oxone-KX



Scheme 2: Plausible mechanism for conversion of an alkyne into a α,α-dihaloketone

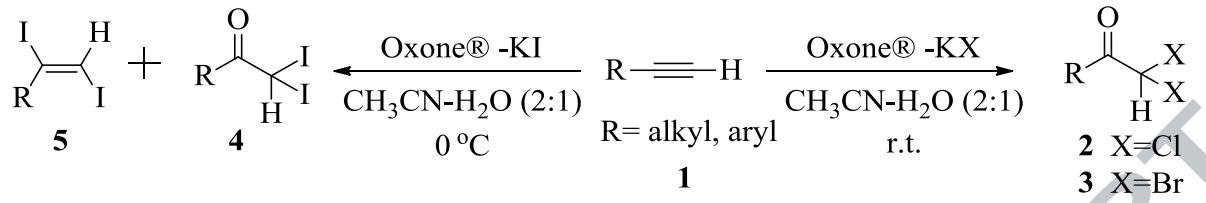
Table 1: A study of various halogen sources for conversion of phenyacetylene into a α,α-dihaloacetophenone using oxone® as the oxidant.



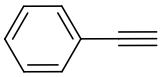
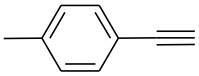
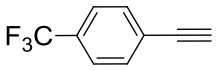
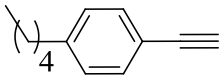
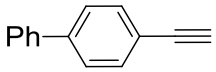
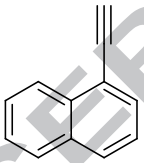
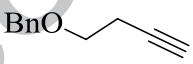
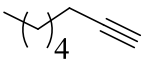
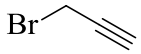
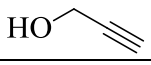
S.No.	Halogen source	Product	Reaction time (min)	% yield[a]
1	50% Aq. HCl		60	66
2	NH_4Cl		60	75
3	NaCl		60	80
4	KCl		10	98
5	48% Aq. HBr		60	50
6	NH_4Br		60	60
7	KBr		15	99
8		N. R.	-	-
9	KI	 3:1	20	99
10[b]	KI	 1:1	20	99

[a]Isolated yields; [b]reaction temperature = -10 °C.

Table 2: Oxyhalogenation of alkynes using Oxone® -KX



5 **4** **1**

Entry	Alkyne **1** R—	**2**		**3**		**4/5**	
		% yield[a]	Reaction Time (min)	% yield[a]	Reaction Time (min)	% yield[a]	Reaction Time (min)
a		98	10	99	15	51/48	20
b		96	15	97	15	52/47	25
c		94	30	95	30	5/94	120
d		96	10	97	30	48/50	20
e		90	20	92	20	50/45	25
f		79	30	82	30	45/52	20
g		87	15	90	20	48/49	20
h		89	20	94	25	46/50	25
i		86	30	89	30	44/48	25
j		80	30	77	30	42/54	30

[a]Isolated yields. All products gave satisfactory ^{1}H&^{13}C NMR, IR and Mass spectral data.