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Oxidative bromination of ketones using ammonium bromide and oxone®

Arun Kumar Macharla, Rohitha Chozhiyath Nappunni, Mahender Reddy Marri, Swamy Peraka, Narender Nama *

I&PC Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A highly efficient, environmentally safe and economic method for selective α-monobromination of aralkyl, cyclic, acyclic, 1,3-diketones and β-keto esters and α,α-dibromination of 1,3-diketones and β-keto esters without catalyst is reported using ammonium bromide as a bromine source and oxone® as an oxidant. The reaction proceeds at ambient temperature and yields range from moderate to excellent. Bromination of unsymmetrical ketones takes place at the less substituted α-position predominantly. Aromatisation of tetralones is also carried out with this reagent system.

The α-bromination of ketones is an important transformation in synthetic organic chemistry.[1] α-Bromoketones are among the most versatile intermediates in organic synthesis and their high reactivity makes them prone to react with large number of nucleophiles to provide a variety of biologically active compounds.[2] α-Bromoacetophenone derivatives have been investigated for their active participation in the inhibition of protein tyrosine phosphatase such as SHP-1 and PTP1B.[3] Bromination at the reactive position in a 1,3-keto compound enhances bioactivity, particularly cytotoxicity against breast cancer 1A9 cells, with respect to the unsubstituted compound.[4]

The most commonly used reagents for α-bromination of ketones include molecular bromine,[5] *N*-bromosuccinimide (NBS)[6] and cupric bromide.[7] Recently, various methods have been reported using NBS–NH_4OAc,[8] NBS-photochemical,[9] NBS–PTSA,[10] NBS–silica supported sodium hydrogen sulfate,[11] NBS–Amberlyst-15,[12] NBS–Lewis acids,[13] NBS–ionic liquids,[14] $MgBr_2$-(hydroxy(tosyloxy)iodo) benzene-MW,[15] *N*-methylpyrrolidin-2-one hydrotribromide (MPHT),[16] $(CH_3)_3SiBr–KNO_3$,[17] BDMS,[18] NaBr.[19]

Reagents used for the bromination of unsymmetrical acyclic ketones are NBS–NH_4OAc,[8] NBS-photochemical,[9] and NBS–PTSA[10] and all these methods provide a mixture of 1-bromo(terminal) and 3-bromo ketones with predominant formation of 3-bromo product. Gaudry and Marquet reported the selective terminal bromination of unsymmetrical acyclic ketone using elemental bromine.[20] From the green chemistry point of view the use of elemental bromine has several environmental drawbacks. The handling of liquid bromine, due to its hazardous nature, is troublesome and special equipment and care is needed for the transfer of these materials in large scale.

Though all these methods provide good yields, most of them suffer from one or more disadvantages such as long reaction times, harsh reaction conditions, use of hazardous chemicals and cumbersome work-up procedures. The use of NBS is a better alternative for molecular bromine, which does not produce HBr in this reaction; but it is expensive and generates organic waste. Furthermore, most of these methods generally employ strongly acidic or basic conditions and accompany undesirable formation of α,α-dibrominated products in significant amount. Hence, the development of an efficient, eco-friendly, atom-economic (100% with respect to bromine) and selective procedure for the α-monobromination of ketones remains a major challenge for synthetic organic chemists.

Oxone® ($2KHSO_5$, $KHSO_4$, K_2SO_4), a potassium triple salt containing potassium peroxy monosulfate, is an effective oxidant. Oxone® is becoming increasingly popular reagent for oxidative transformations[21–25] due to its stability, water solubility, ease of transport, nontoxic 'green' nature, safety profile, cost-effectiveness and non-polluting byproducts.

In continuation of our work on the application of NH_4Br/oxone® system,[26] we wish to explore the applicability of this reagent system for the bromination of ketones. Herein, we report the bromination of various ketones such as aralkyl, cyclic, acyclic, 1,3-diketones and β-keto esters at room temperature (or reflux temperature) without the use of catalyst.[27] However, to the best of our knowledge bromination of ketones using NH_4Br/oxone® system has not been previously reported.

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* Corresponding author. Tel.: +91 40 27191703; fax: +91 40 27160387/757.
E-mail address: narendern33@yahoo.co.in (N. Nama).

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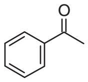
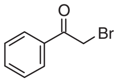
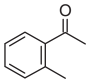
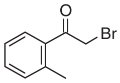
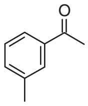
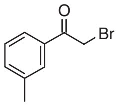
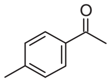
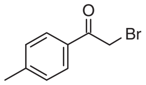
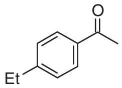
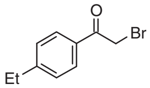
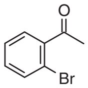
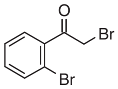
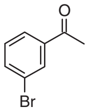
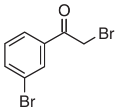
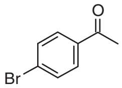
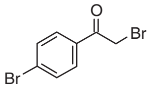
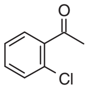
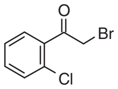
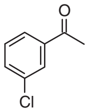
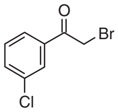
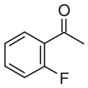
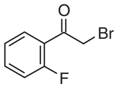
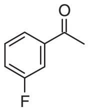
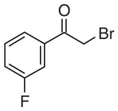
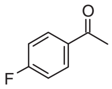
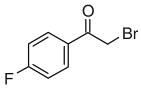
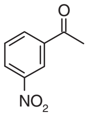
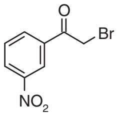
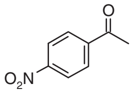
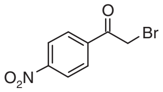
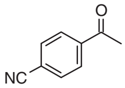
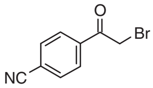
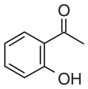
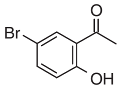
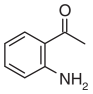
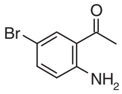
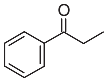
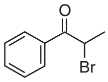
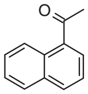
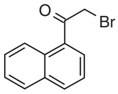
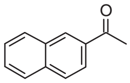
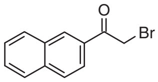
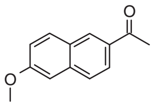
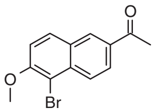
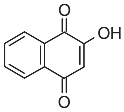
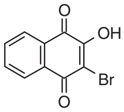
Table 1
Bromination of aralkyl ketones using NH_4Br and oxone®[a]

Entry	Substrate	Time	Product	Yield[b] (%)
1		7 h^c 15 min^d	 **1a**	81 97
2		26 h^c 2.5 h^d	 **1b**	92 91
3		24 h^c 40 min^d	 **1c**	84 96
4		6 h^c 2.5 h^d	 **1d**	63 94
5		7 h^c 1.5 h^d	 **1e**	54 86
6		48 h^c 4 h^d	 **1f**	42 56
7		48 h^c 2 h^d	 **1g**	37 (28)^e 73
8		48 h^c 1.5 h^d	 **1h**	37 98
9		48 h^c 3 h^d	 **1i**	50 73
10		47 h^c 2 h^d	 **1j**	49 87
11		24 h^c 2 h^d	 **1k**	81 85
12		24 h^c 2 h^d	 **1l**	39 (34)^e 83
13		44 h^c 1.3 h^d	 **1m**	89 97
14		48 h^c 3 h^d	 **1n**	14 (16)^e 46 (14)^e
15		24 h^c 1.5 h^d	 **1o**	8 (12)^e 21 (34)^e
16		48 h^c 16 h^d	 **1p**	38 35 (6)^e
17		4.5 h^c 1.5 h^d	 **1q**	61 (26)^f 48 (28)^f
18		1 h^c 5 min^d	 **1s**	93 83
19		26 h^c 7.5 h^d	 **1t**	10 58
20		24 h^c 1.25 h^d	 **1u**	39 87
21		24 h^c 20 min^d	 **1v**	60 97
22		40 min^c 10 min^d	 **1w**	97 94
23		3 h^c 15 min^d	 **1x**	98 98

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[a] Reaction conditions: Substrate (2 mmol), NH_4Br (2.2 mmol), oxone® (2.2 mmol), methanol (10 ml), room or reflux temperature.

[b] The products were characterized by ^1H NMR, Mass spectra and quantified by GC.

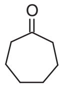
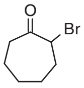
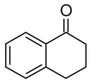
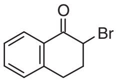
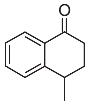
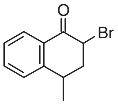
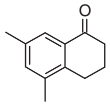
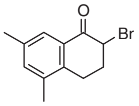
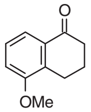
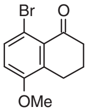
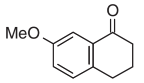
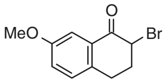
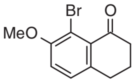
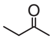
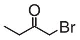
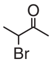
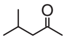
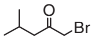
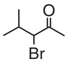
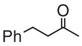
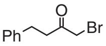
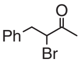
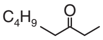
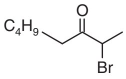
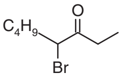
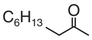
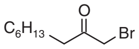
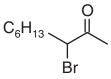
[c] Room temperature.

[d] Reflux temperature.

[e] α-Bromo dimethyl ketal.

[f] 3-Bromo-2-hydroxyacetophenone (**1r**).

Table 2
Bromination of various cyclic and acyclic ketones using NH_4Br and oxone[a]

Entry	Substrate	Time	Product (Yield[b] (%))
1		2 h[c] 30 min[d]	 (65) (80) **2a**
2		6 h[c] 20 min[d]	 (92) (98) **2b**
3		28 h[c] 2 h[d]	 (77) (77) **2c**
4		6 h[c] 20 min[d]	 (79) (95) **2d**
5		2 h[c] 20 min[d]	 (90) (87) **2e**
6		2.5 h[c] 1 h[d]	 (17) (42) **2f**  (42) (18) **2g**
7		8 h[c]	 (80) **2h**  (09) **2i**
8		7 h[c] 5 min[d]	 (90) (85) **2j**  - (06) **2k**
9		5 h[c] 30 min[d]	 (65) (71) **2l**  (10) (21) **2m**
10		9 h[c] 1 h[d]	 (62) (55) **2n**  (37) (44) **2o**
11		7 h[c] 20 min[d]	 (71) (76) **2p**  (28) (23) **2q**

[a] Substrate (2 mmol), NH_4Br (2.2 mmol), oxone® (2.2 mmol), methanol (10 ml).
[b] The products were characterized by ^1H NMR, Mass spectra and quantified by GC.
[c] Room temperature.
[d] Reflux temperature.

Initially, the effect of different solvents on the α-bromination of acetophenone was studied using NH_4Br/oxone® system. In methanol at room temperature, the reaction completed within 7 h to give the α-brominated product in an 81% yield together with recovery of the starting material. The reaction in CH_3CN, H_2O gave less than a 15% yield after 7 h and in case of other solvents (DCM, $CHCl_3$, CCl_4, EtOH, hexane, ether and THF) the yields were negligible. Among the solvents used, methanol appeared to be the most suitable in terms of maximum yield.

With the optimized conditions in hand, a variety of aralkyl ketones (acetophenone, substituted acetophenones, acetonaphthone and substituted acetonaphthones) were subjected to the bromination reaction to test the generality of this method and the results are summarized in Table 1. All the reactions were performed using 2 mmol of substrate with 2.2 mmol of NH_4Br and 2.2 mmol of oxone® in 10 ml methanol at room temperature (or reflux temperature).

It is interesting to mention the effect of reaction temperature on course of bromination, high yields are obtained at reflux temperature in short reaction time compared to room temperature. In order to determine the influence of the substitution on aromatic ring on the reaction path with this reagent system, we studied the reaction with different substitutions on phenyl ring of acetophenone and acetonaphthones. Presence of highly activating groups (Table 1, entries 17, 18 and 22) on phenyl ring favours nuclear bromination, whilst moderately activating and deactivating groups favours the α-bromination (Table 1, entries 2–13). Strong electron-withdrawing groups (Table 1, entries 14 and 15) present on phenyl ring gave α-brominated product, along with substantial amount of α-bromo dimethyl ketals. Propiophenone gave the α-brominated product with this reagent system, but yield was less even after longer reaction time (Table 1, entry 19). 2-Hydroxy-1,4-naphthoquinone showed good reactivity with this reagent system and gave 3-bromo-2-hydroxy-1,4-naphthoquinone (**1x**) in high yield within short reaction time (Table 1, entry 23).

Further, we studied the bromination of cyclic and acyclic ketones under similar reaction conditions and results are summarized in Table 2. Cyclic ketones are reacted well under the present reaction condition to furnish corresponding α-bromo ketone in good to excellent yields, except 5-methoxy and 7-methoxytetralone. 5-Methoxytetralone afforded the respective ring brominated product (**2e**) selectively and 7-methoxy-1-tetralone at room temperature forms the corresponding α-brominated (**2f**) and ring brominated (**2g**) products in the ratio of 17:42 in 2.5 h and the same reaction at reflux temperature afforded a 42:18 ratio within 1 h.

Interesting results were observed when unsymmetrical acyclic ketones subjected to the bromination with this reagent system. On contrary to the earlier reports[8–10], bromination took place at less substituted α-position predominantly (Table 2, entries 7–11).

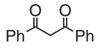
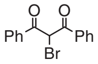
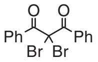
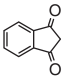
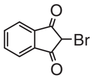
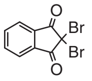
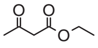
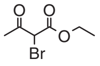
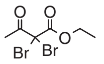
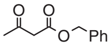
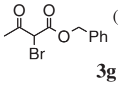
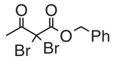
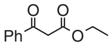
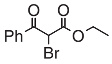
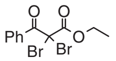
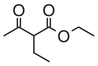
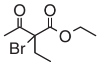
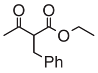
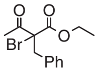
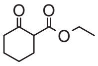
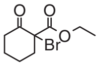
Finally, we investigated the bromination of 1,3-dicarbonyl compounds under similar reaction conditions. A variety of α-unsubstituted 1,3-diketones and β-keto esters were α-mono brominated and α,α-dibrominated using NH_4Br and oxone® with excellent yields (Table 3, entries 1–5). Similarly, α-substituted-β-keto esters underwent α-bromination smoothly under similar conditions and afforded the corresponding α-brominated product in high yields (Table 3, entries 6–8).

Different results were observed in case of tetralone depending on the solvent. The α-brominated product (**2b**) was obtained in MeOH whilst the corresponding dehydrogenated product, that is 1-naphthol (**7**), was formed in DCM, 1 equiv of tetralone with 1.1 equiv of NH_4Br and 1.1 equiv of oxone® in DCM yielded 65% of **7**, with 2.2 equiv of NH_4Br yielded 90% of **7**. In case of substituted tetralones (**5** and **6**) side products **8** and **9** were also observed (Scheme 1).

We propose a plausible reaction mechanism for the α-bromination of ketones as shown in Scheme 2. It is assumed that oxidation of bromide ion by peroxymonosulfate ion could give the hypobromite ion, which in turn reacts with ketones to afford α-brominated ketones.

In conclusion, we have developed a novel and efficient approach for the mild α-bromination of various ketones and 1,3-dicarbonyl compounds and α, α-dibromination of 1,3-dicarbonyl compounds using NH_4Br and oxone® without catalyst, avoiding the use of conventional reagent NBS for this transformation. The noteworthy feature of the present method is the use of NH_4Br/oxone® system as a mild, non-toxic, inexpensive reagent coupled with simple operation and formation of cleaner products with high yields. Another notable benefit of this system is that, unsymmetrical acyclic ketones brominated at less substituted α-position predominantly.

Table 3
Bromination of 1,3-dicarbonyl compounds using NH_4Br and oxone®

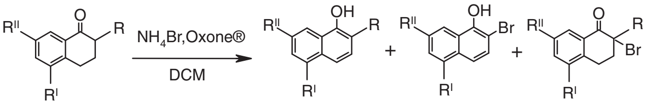
Entry	Substrate	Time	Product (Yield[a] (%))	
1		40 min[b] 30 h[c]	 (94) - **3a**	 - (90) **3b**
2		1 h[b] 40 min[d]	 (80) - **3c**	 (10) (95) **3d**
3		3 h[b] 30 min[d]	 (75) - **3e**	 (24) (94) **3f**
4		35 min[b] 30 min[d]	 (81) - **3g**	 (18) (96) **3h**
5		30 min[b] 3 h[c]	 (90) - **3i**	 (09) (94) **3j**
6		9 h[b]	 (70) **3k**	
7		5 h[b]	 (87) **3l**	
8		30 min[b]	 (95) **3m**	

[a] The products were characterized by ^1H NMR, Mass spectra and quantified by GC.

[b] Substrate (2 mmol), NH_4Br (2.2 mmol), oxone® (2.2 mmol), methanol (10 ml), room temperature.

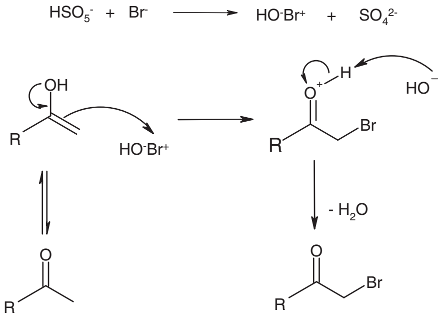
[c] Substrate (2 mmol), NH_4Br (4.4 mmol), oxone® (4.4 mmol), methanol (10 ml), reflux temperature.

[d] Room temperature.



	7	8	9
4 R = H, R' = H, R'' = H	90	-	-
5 R = H, R' = Me, R'' = Me	31	8	17
6 R = Me, R' = H, R'' = H	27	-	8

Scheme 1. Aromatization of tetralones.



Scheme 2. Plausible reaction mechanism.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, ^{1}H NMR and Mass spectral data of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.011.

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27. *General procedure for the bromination of carbonyl compounds*: Oxone® (1.352 g, 2.2 mmol) was added to the well stirred solution of substrate (2 mmol) and NH_4Br (0.215 g, 2.2 mmol) in methanol (10 ml) and the reaction mixture was allowed to stir at room temperature (or reflux temperature). After completion of the reaction, as monitored by TLC, the reaction mixture was quenched with aqueous sodium thiosulfate, and extracted with ethyl acetate (3 × 25 ml). Finally, the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and removal of solvent in vacuo yielded a crude residue, which was further purified by column chromatography over silica gel (finer than 200 mesh) to afford pure products. All the products were identified on the basis of ^{1}H NMR and mass spectral data.