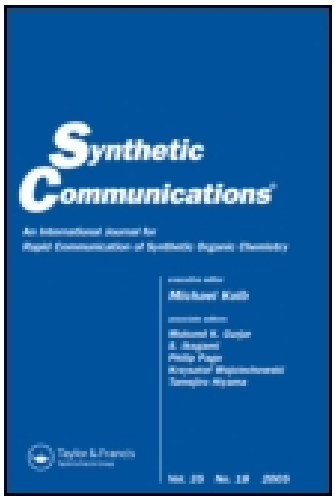

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Studies on Bromination of Active Methylene by a Mixture of Hydrobromic Acid and Hydrogen Peroxide (or TBHP)

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ABSTRACT

Studies on bromination of active methylene with a mixture of hydrogen peroxide or *tert*-butylhydroperoxide (TBHP) and hydrobromic acid are discussed. Substituted acetophenones, benzocyclic ketones provide α-bromo-keto compounds in high yields under this reaction condition.

Key Words: Oxyhalogenation; Active methylene; H_2O_2; TBHP; HBr.

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We have reported[1] a simple and efficient protocol for the halogenation of arenes, alkenes, and alkynes using a combination of hydrohalic acid and hydrogen peroxide or *tert*-butylhydroperoxide (TBHP).

During the studies on the oxyhalogenation of variously substituted arenes using our protocol[1] when acetophenone was subjected to bromination reaction, side chain bromination was preferred over aromatic bromination. The scope and generality of this observation is discussed in the present communication.

RESULTS AND DISCUSSION

Table 1 depicts the results of bromination of active methylenes (α- to keto group) in substituted acetophenones. It was found that they undergo α-bromination (Table 1, Entries 1–7) in high yields using hydrogen peroxide or TBHP as oxidants.

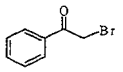
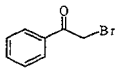
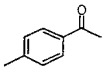
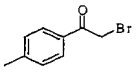
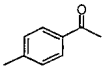
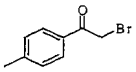
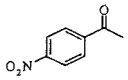
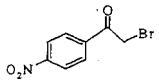
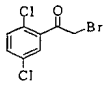
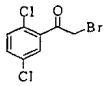
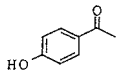
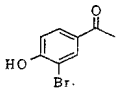
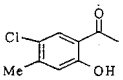
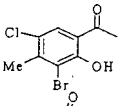
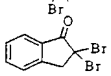
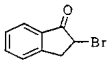
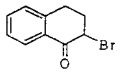
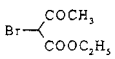
However, acetophenones with free hydroxyl function (phenolic, Entries 8 and 9) resulted into aromatic bromination, which is in agreement with our earlier[1] observation. TBHP exhibited excellent selectivity for monobromination in case of cyclic ketones (Sch. 1) viz. indanone and tetralone (Entries 11 and 12) whereas H_2O_2 was required in large excess (Entry 10) for completion of reaction which furnished the dibrominated product as the single product in 89% yield. The reagent was found to be selective for bromination of active methylene as no bromination of benzylic positions was observed. Similar difference in the activity of the oxidants was observed and discussed in our previous publications. It is noteworthy that bromination of ethyl acetoacetate could be controlled (Entry 13) to obtain only monobrominated product in 99% yield in the presence of several vulnerable positions for bromination.

EXPERIMENTAL

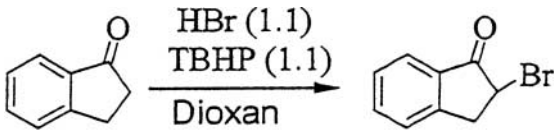
General Procedure

Progress of reactions was monitored by TLC using Merck silica gel 60 F254 precoated plates and spots were visualized under UV light or on exposure to I_2 vapors. NMR spectra were recorded at 200 MHz in $CDCl_3$ using TMS as internal standard. Hydrogen peroxide (30% w/v) was procured from Asian chemicals, India and *tert*-butylhydroperoxide (TBHP, 70% w/v) was obtained from Aldrich Chemicals, India.

Table 1.

Entry	Substrate	Reaction condition	Product	% yield[a]
1		Dioxan HBr (1.5) H_2O_2 (1.1)		95
2		Dioxan HBr (1.1) TBHP (1.1)		85
3		Dioxan HBr (1.1) H_2O_2 (1.1)		93
4		Dioxan HBr (1.1) TBHP (1.1)		87
5		Dioxan HBr (1.5) H_2O_2 (1.1)		75
6		Dioxan HBr (1.1) H_2O_2 (1.1)		94
7		Dioxan HBr (1.1) TBHP (1.1)		90
8		Dioxan HBr (1.5) H_2O_2 (1.1)		90
9		Dioxan HBr (1.2) H_2O_2 (1.1)		98
10		Methanol HBr (4.0) H_2O_2 (4.0)		89
11		Dioxan HBr (1.1) TBHP (1.1)		65
12		Dioxan HBr (1.1) TBHP (1.1)		64
13		CH_2Cl_2 HBr (1.5) H_2O_2 (1.1)		99

[a]Isolated yield, characterized by usual spectral analysis.



Scheme 1.

Aqueous hydrobromic acid (47%) was purchased fiom S.D. Fine Chemicals, India.

Preparation of 2 Bromo-1-(4-methylphenyl)-l-ethanone (Table 1: Entry 4)

A solution of TBHP (70% aq. 0.25 mL 2 mmol) was added to a cooled mixture of HBr (48% aq. 0.34 mL, 2 mmol) in dioxan (5 mL) and the mixture stirred for 5 min. To this cold solution 4-methylphenyl-1-ethanone (0.268 g, 2 mmol) was added, stirred at same temperature for 30 min and then refluxed for 20 h. On completion of reaction (TLC) the solvent was evaporated and the product was taken in 5 mL water, extracted with EtOAc (3×10 mL) washed with water and brine, dried on sodium sulphate and concentrated on rotary evaporator to afford a yellowish solid. The product was purified by flash colum chromatography over silica gel to afford pure product (0.370 g, 86.85%). IR: ν 2991.83, 2922, 1659, 1583, 1171, 650 cm^{-1}, ^{1}H NMR: ($CDCl_3$) δ 2.4 (s, 3H) 4.4 (s, 2H), 7.22–7.27 (m, 2H), 7.84 (m, 2H). MS (m/z): 212 (M+), 164 (20), 119 (100), 105 (20), 91 (100), 77 (20), 65 (50). Elemental analysis: Calculated for C_9H_9BrO, C: 50.70, H: 4.22, Br: 37.08, Found C: 51.25, H: 4.29, Br: 37.06.

In conclusion we have demonstrated regioselective bromination of active methylene in high yields by applying a combination of hydrobromic acid and hydrogen peroxide or TBHP under mild reaction condition in high yield. This method provides simple work-up, easy purification and economical process for industrial applications.

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