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KH_2PO_4 as a novel catalyst for regioselective monobromination of aralkyl ketones using *N*-bromosuccinimide: a green methodology

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Abstract: A simple, regioselective and green method has been developed for the preparation of monobrominated ketones from various aralkyl ketones by using *N*-bromosuccinimide in presence of KH_2PO_4 in EtOH at reflux temperature. The present method is of short reaction time and simple with excellent isolated yields of products. The use of eco-friendly solvent, reuse of organic waste (succinimide) and recyclable catalyst used for 4 times without loss of activity are advantageous. This is the first example of the use of KH_2PO_4 as a useful catalyst in organohalogen chemistry and the present method meets reduce-reuse-recycle (RRR) principle towards development of green protocol.

Keywords: Regioselectivity; bromination; ketones; KH_2PO_4; Heterogeneous catalysis; Green method; succinimide; H_2O_2-HBr.

1. Introduction

Development of the simple, efficient and environmental friendly synthetic methodologies for the commonly used small organic molecules is one of the major challenges in modern organic synthesis. It is renowned that *N*-bromosuccinimide (NBS) is a superior brominating agent[1] and it is a better alternative for molecular bromine which does not produce HBr in the reaction. Extensive literature studies reveal that a number of bromination protocols for the bromination of carbonyl compounds have been reported and it is known that the conditions employed for bromination become favorable with the advent of suitable catalysts and co-catalysts. The selective α–bromination of the side chain of the ketones is reported[2-13] and nuclear bromination of aromatic rings is also reported[14-18]. Several brominated compounds are found to be valuable key starting materials in organic syntheses of industrially important and biologically active anti-viral, anti-fungal, anti-bacterial, anti-neoplastic and anti-tumor compounds[19-21].

Though all these methods provided good yields, most of them endure from one or more disadvantages such as long reaction times, use of hazardous chemicals, precarious operational procedures and generating organic waste (succinimide) in large quantities. The method become greener and more productive if the by-product, succinimide is able to separate from the reaction mixture during work-up and its subsequent usage as substrate for the synthesis of NBS or other biologically active succinimide derivatives[22]. Hence, the development of user-friendly and eco-friendly method for regioselective monobromination of ketones remains a major challenge for

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synthetic organic chemists. KH_2PO_4 is known to be easily available, inexpensive, ecologically favorable and safe to handle. It can be removed after reaction by simple filtration and can be reused for 4 times without loss of activity. In fact, KH_2PO_4 has been used as a heterogeneous catalyst[23] for very limited synthetic transformations.

In continuation of our research on evaluating the role of various inorganic substances as catalysts for the bromination of ketones using NBS[7-9], herein we report an environmentally benign procedure for regioselective monobromination of ketones (Figure 1) using NBS in EtOH in the presence of 10% KH_2PO_4. In addition, we report a re-preparation of NBS from succinimide, by-product, by oxidation with HBr-H_2O_2 system. (Figure 2).

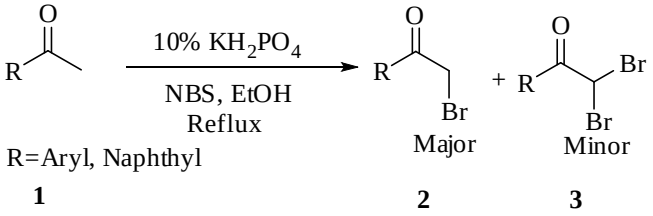


Figure 1. Synthesis of α-brominated ketones

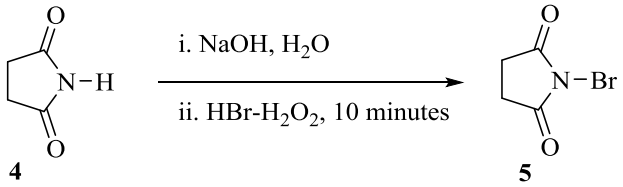


Figure 2. Synthesis of NBS from by-product, succinimide

2. Results and discussion

In general, acetophenone is used for the evaluation of various bromination methods with respect to optimization of reaction conditions, for example mono *versus* disubstitution or ring functionalization.[25]

2.1. Role of catalyst:

Initially, we studied the effect of catalyst on the course of α-bromination of acetophenone. A reaction was carried out in the absence of catalyst at room temperature and found to be unsuccessful (entry 1, Table 1), while in the presence of 10% KH_2PO_4, the α-bromination is successful with 96% of α-brominated product (**2a**) formation within 10 minutes at reflux temperature (entry 3) in EtOH. However, at 25-30°C (entry 2), lower selectivity is observed and 52% of α-brominated product (**2a**) was formed, accompanied by 29% of unreacted substrate **(1a)**.

Table 1. Optimization conditions [a]

Entry	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)
1	-	25-30	24	0
2	KH_2PO_4	25-30 (RT)	7	52
3	KH_2PO_4	Reflux	10 min	96

[a]**Reagents and conditions:** Acetophenone (10 mmol), NBS (11 mmol)-portion wise addition (6 portions), 10% (w/w) KH_2PO_4 catalyst, Ethanol (10 mL).
[b]Isolated yield

2.2. Effect of solvent:

The role of solvent has been examined during the course of bromination. As evident from Table 2, the conversion of acetophenone in different solvents occurred in the following order EtOH > MeOH >Et_2O>THF. It is found that lower yields are obtained with Et_2O and THF (entries 1, 2). In MeOH, lower yields i.e. 61% and 82% of product **(2a)** are obtained (entry 3) both at lower (RT) and higher (reflux) temperatures, respectively. In contrast, EtOH provided excellent isolated yields (96%) of product **(2a)** at reflux temperature compared to room temperature (52%) (entry 4).

Table 2. Effect of solvent[a]

Entry	Solvent	Temp (°C)	Time	Yield[b] (%)
1	Et_2O	25-30	2 h	24
		Reflux	30 min	32
2	THF	25-30	4 h	18
		Reflux	20 min	35
3	MeOH	25-30	5 h	61
		Reflux	25 min	82
4	EtOH	25-30	7 h	52
		Reflux	10 min	96

[a]**Reagents and conditions:** Acetophenone (10 mmol), NBS (11 mmol), 10% (w/w) KH_2PO_4 catalyst, solvent (10 mL).
[b] Isolated yield.

2.3. Effect of temperature:

As evident from the above study, EtOH is the best option for maximum yield of desired product under KH_2PO_4 catalyst conditions. Further, the effect of temperature on the course of bromination is investigated. In general, at higher temperature selectivity will be lost and further bromination leads to improved formation of dibrominated product. But, a diverse situation is observed in the present case i.e. increase of temperature (up to reflux) provided improved yields of the desired product (**2a**) in EtOH. For example, at reflux, the formation of monobrominated product **(2a)** is increased (96%) (entry 6, Table 3). While, at moderate temperatures (i.e. 30-40°C, 40-50°C, 50-60°C & 60-70°C), the formation of significant amount of dibrominated product **(3a)** is observed (entries 2-5). At lower temperature (20-30°C), the rate of the reaction is sluggish (8 h) with lower yields (entry 1) of product **(2a)** with enhanced dibrominated product **(3a)** formation (entry 1) as well as presence of unreacted substrate.

Table 3. Effect of temperature[a]

Entry	Temp (°C)	Time (hrs)	Yield[b] (%)
1	20-30	8	53
2	30-40	5	65
3	40-50	2	71
4	50-60	1.5	76
5	60-70	1	80
6	Reflux	10 min	96

[a]**Reaction conditions:** Acetophenone (10 mmol), NBS (11mmol)-portion wise addition (6 portions), 10% (w/w) KH_2PO_4 catalyst, Ethanol (10 mL).
[b]Isolated yield.

2.4. Effect of mode of addition of N-bromosuccinimide:

The mode of NBS addition has significant effect on isolated yield of product. For example, portion wise addition of NBS leads to improved yields (entries 2-4, Table 4) of monobrominated product **(2a)** due to controlled release of bromonium ion compared to one time addition (entry 1).

Table 4. Effect of mode of addition of NBS[a]

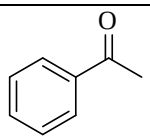
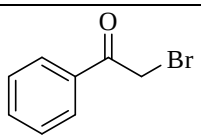
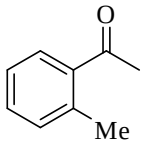
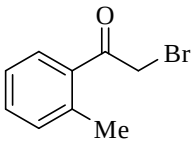
Entry	NBS addition mode	Time (min)	Yield[b] (%)
1	Once	7	66
2	2 portions	10	73
3	4 portions	13	84
4	6 portions	15	96

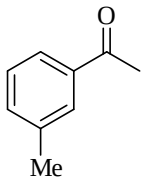
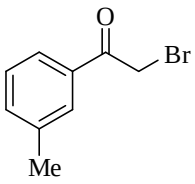
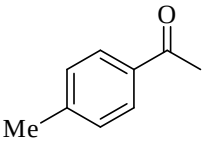
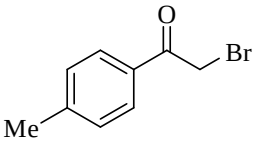
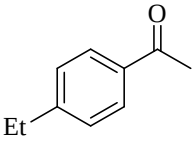
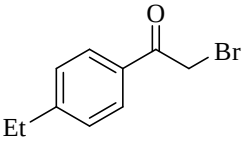
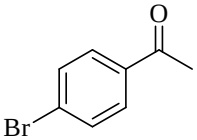
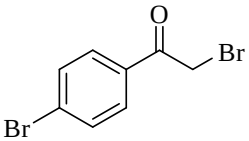
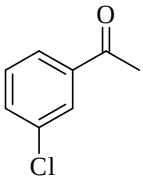
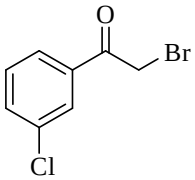
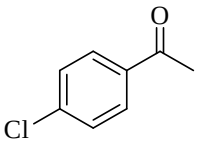
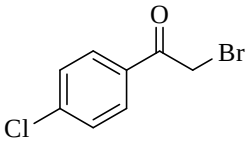
[a]**Reaction conditions:** Acetophenone (10 mmol), NBS (11 mmol), 10% (w/w) KH_2PO_4, Ethanol (10 mL) at reflux temperature.
[b]Isolated yield.

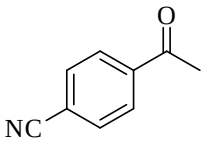
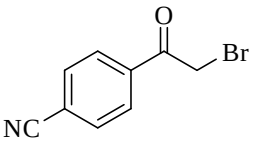
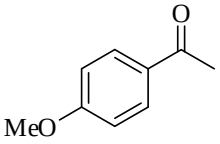
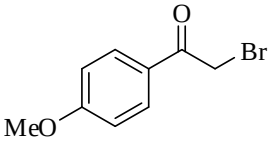
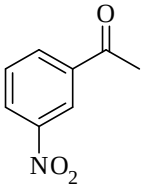
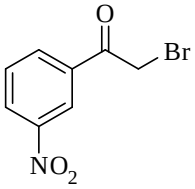
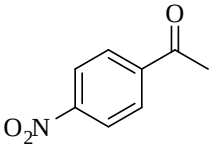
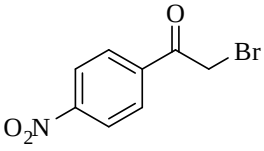
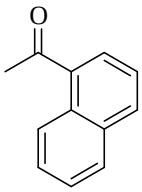
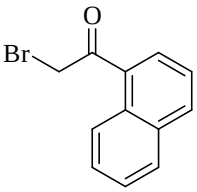
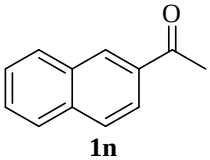
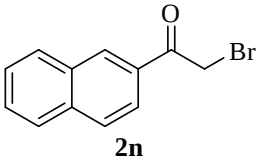
2.5. Scope of the method:

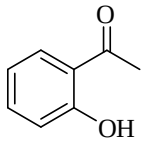
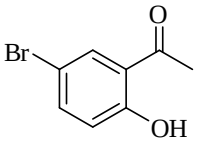
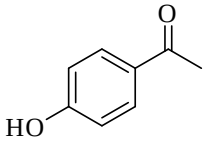
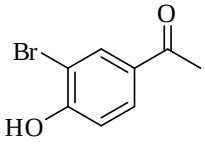
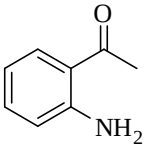
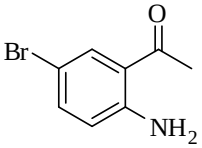
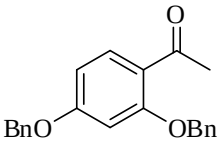
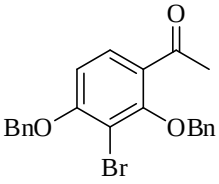
The effect of substrate structure is studied with the help of well optimized conditions using a variety of ketones (acetophenone, substituted acetophenones and acenaphthones) to examine the generality of this process and the obtained results are summarized in Table 5. Consistent with the acquired results, it is found that substrate bearing moderate activating group provided excellent yields of products (entries 2-9, Table 5). In contrast, presence of high deactivating groups afforded lower yields of desired products (entries 11-12). The acenaphthones undergo α-bromination and provided good yields of desired products (entries 13, 14). Interestingly, substrates with high electron donating groups afforded ring brominated products, exclusively (entries 15-18). But the *p*-methoxy acetophenone undergoes exclusively α-bromination instead of nuclear bromination even though it contains high activating group –OMe (entry 10).

Table 5. Synthesis of mono brominated aralkyl ketones (α-bromination *Vs* ring bromination) using KH_2PO_4 catalyst[a]

Entry	R	Product	Time (min)	Yield[b] (%)	Lit. Ref.
1	 **1a**	 **2a**	10	96	[7-9]
2	 **1b**	 **2b**	17	90	[7-9]

3	 **1c**	 **2c**	16	93	[7-9]
4	 **1d**	 **2d**	14	96	[7-9]
5	 **1e**	 **2e**	16	88	[7-9]
6	 **1f**	 **2f**	17	87	[7-9]
7	 **1g**	 **2g**	15	80	[7-9]
8	 **1h**	 **2h**	18	91	[7-9]

9	 **1i**	 **2i**	17	58	[7-9]
10	 **1j**	 **2j**	16	77	[7-9]
11	 **1k**	 **2k**	18	46	[7-9]
12	 **1l**	 **2l**	20	54	[7-9]
13	 **1m**	 **2m**	18	88	[7-9]
14	 **1n**	 **2n**	19	94	[7-9]

15	 **1o**	 **2o**	12	74	[7-9]
16	 **1p**	 **2p**	13	94	[7-9]
17	 **1q**	 **2q**	11	68	[7-9]
18	 **1r**	 **2r**	10	98	[7-9]

[a]**Reaction conditions:** substrate (10 mmol), NBS (11mmol), 10% (w/w) KH_2PO_4, Ethanol (10 mL).
[b] Isolated yield.

3. Experimental Section

3.1. Chemicals and Apparatus:

All melting points are uncorrected. All chemicals used are of reagent grade and used as received without further purification. Ketones are purchased from Merck and s.d. Fine Chemicals Ltd., Mumbai, India. *N*-bromosuccinimide is purchased from Merck Mumbai, India. Absolute EtOH (99.9%) is purchased from Changshu Yangyuan Chemical, China. The double distilled water is used for work-up. Melting points are determined and are uncorrected. ^{1}H NMR spectra are recorded on a Varian 300 MHz NMR. Chemical shifts are expressed in parts per million (ppm). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Mass spectra (MS) is acquired on Agilent, model-6410, triple quard LC-MS. Thin-layer chromatography is performed on 0.25 mm Merck silica gel plates (60F-254) and detected under UV light. Column chromatography is performed on silica gel (100-200 mesh, Merck).

3.2. Typical procedure for monobromination of ketone(s):

A mixture of ketone (10 mmol) and 10% KH_2PO_4 catalyst in EtOH (10 mL) were taken in 100-mL RB flask and the temperature was raised to reflux. Then, NBS (11 mmol) was added portion wise (6 portions). After completion of the reaction, as evident by TLC, the reaction mixture was filtered off to

remove the catalyst from the reaction mixture and the solvent was removed under vacuum. Further, Et_2O was added to the reaction mixture and organic phase was extracted (succimide, side product, is insoluble in Et_2O). Finally, the organic layer was collected and solvent was removed using rotary evaporator. The obtained crude product was purified by column chromatography over silica gel using mixture of n-hexane and EtOAc (99:1 ratio) to obtain pure product (**2**).

3.3. Recovery of by-product, succinimide and subsequent utilization for NBS production:

The succinimide, a by-product of *N*-bromosuccinimide based reactions is being dumped into environment and it may leads to serious harm to the environment. To prevail over this issue, it was recovered and reused for the synthesis of NBS using green brominating agent of H_2O_2-HBr system.[24]

3.3.1. Procedure for synthesis of NBS using the by-product, Succinimide:

Bromine was generated by mixing 48% aqueous solution of HBr (1.60 mL, 14.0 mmol) with 30% aqueous solution of H2O2 (2.86 mL, 28.0 mmol) in water (7.0 mL) at RT in a RB flask-1 covered with aluminium foil.24 In RB flask-2, the by-product, succinimide (0.99 gm,10.0 mmol) was dissolved in water, added NaOH (0.4 gm, 10.0 mmol) and stirred for 5 minutes at 2-5°C. It was then added slowly to the RB flask-1 and stirred for 20 minutes at 2-5°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to -15°C, added 5 vol of Isopropyl alcohol (IPA), stirred well, filtered and washed with cold IPA. The obtained N-bromosuccinimide was dried in desiccator and reused for bromination of ketones. Yield: 70%, m.p.173-175°C.

3.4. Specification(s) of KH_2PO_4 Catalyst:

The KH_2PO_4 has the following characteristics. It is commercially available white crystalline solid, pH value (5% in water): 4-5; Assay: 98%, Merck made, India.

3.4.1. Reuse of Catalyst:

On reuse of KH_2PO_4 catalyst for α–bromination of acetophenone provided yields of 96%, 94%, 90% and 84% of product (**2a**) for the first, second, third and fourth recycle, respectively.

4. Conclusion

In summary, ketones are regioselectively monobrominated using NBS in EtOH in presence of 10% KH_2PO_4, with good to excellent isolated yields of the desired products within a short period of time (10-20 minutes. This approach increased the selectivity of monobromination *vs.* dibromination. Other superior features of this protocol include the use of inexpensive and easily available catalyst which doesn't entail any chemical treatment or activation, efficient optimization of reaction conditions, easy work-up procedure and operationally simple protocol, use of eco-friendly solvent and the formed succinimide as by-product is efficiently reused by the oxidation to NBS. Hence, the present method is the best choice for the synthesis of monobrominated aralkyl ketones as key synthetic precursors in organic syntheses.

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