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An efficient solvent-free selective bromination of ketones by H_2O_2-HBr

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Abstract: Several ketones were successfully brominated by an operationally simple and green procedure under mild, solvent-free and organic waste-free conditions with an aqueous H_2O_2–HBr system. The use of LiCl as a natural catalyst would significantly increases yield and reduces reaction time.

Keywords: α-Bromination; Ketones; Ketamine; Solvent-free.

Introduction

α-Bromination of ketones is one of the attractive and important pathways in organic synthesis. This protocol provides an easy access for compounds that plays an important role as an intermediate for the design of pharmaceuticals and organic materials. Various brominating agents for this purpose have been developed, including molecular bromine [1], *N*-bromosuccinimide (NBS) [2], tetralkylammonium tribromides [3], bromotrimethylsilane-nitrate salt [4], dioxane–dibromid [5], HTIB-$MgBr_2$ [6], *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) [7]. The use of molecular bromine was limited, due to the nature hazardous, low selectivity, generating toxic and corrosive hydrogen bromide, corrosive side products that create separation disposal problems at the end, leading to environmental pollution. Other brominating agents have been increasingly used for α-bromination of carbonyl compounds resulting in easier handling, availability and increased selectivity of the reaction, but they are expensive and have some drawbacks such as solvent requirement, harsh reaction condition, low yield, and lead to organic wastes. Oxidative-bromination with hydrogen peroxide is among the most popular systems for the bromination of organic compounds [8] since H_2O_2 is less expensive than other brominating reagents. Also, water is the only waste generated in the process. However, there are few reports on the Oxidative–Bromination of ketones using H_2O_2. Recently, khan et al. reported that various ß-keto esters and 1, 3-dikeones were successfully brominated by using a combination of vanadium pentoxide, hydrogen peroxide and ammonium [9]. Then J. Iskra et al. reported bromination of various ketones by an aqueous H_2O_2-HBr system without a catalyst under mild, organic solvent-free and organic waste-free conditions with high selectivity for monobromination vs. dibromination [10]. Herein, we report an operationally simple and safe procedure for bromination of ketones with a new condition by an aqueous H_2O_2-HBr system catalyzed by LiCl in high yield at less reaction time and without requirement to solvent in organic waste-free condition.

Results and discussion

In the course of our studies for the synthesis of some ketamine[1a] analogs and a number of bromoketones, needed as starting materials, we examined various brominating reagents for the bromination of ketones under different reaction conditions to achieve the best yield and less reaction time. First, cyclohexylphenyl ketone **1** was chosen as a model for bromination (Table **1**, entries 1-4). All reagents gave more or less the same yield under different reaction condition.

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Table 1. Bromination of cyclohexyphenyl ketone under different reaction conditions.

Entry	Brominating agent	Solvent	Temp °C	Time (h)	Yield[a] (%)
1	NBS-NH_4OAc	Et_2O	rt	16	65%
2	NBS-NH_4OAc	CCl_4	Reflux	8	65%
3	NBS-$NaHSO_4$ SiO_2	Et_2O	rt	5	70%
4	H_2O_2-HBr[b]	H_2O	rt	48	80%
5	H_2O_2-HBr[c]	-	rt	48	83%
6	H_2O_2-HBr	-	70 °C	5	87%

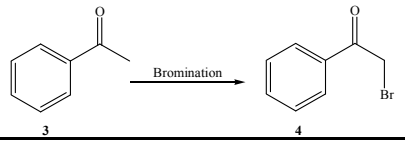
[a] isolated yield.
[b] 1.1eq. HBr (47%) and 2eq. H_2O_2 (30%) were added to ketone in water in four portions.
[c] 1.1eq. HBr (47%) and 2eq. H_2O_2 (30%) were added to ketone in one portions.

Since bromination of ketone **1** with H_2O_2-HBr resulted in the best yield, this approach was considered for the preparation of bromoketones. To avoid long reaction times, the effects of solvent and temperature on the same reaction were investigated to achieve less reaction time and higher yield.

Then, bromination of cyclohexylphenyl ketone **1** in the presence of 2eq H_2O_2 and 1.1eq HBr without water, as solvent, in one step, was investigated and 83% yield was obtained after 48h at room temperature (entry 5). Interestingly, when the same reaction was carried out at 70 °C (entry 6), 87% yield was obtained after 5h. This promising result led us to conclude that higher reaction temperature reduces reaction time.

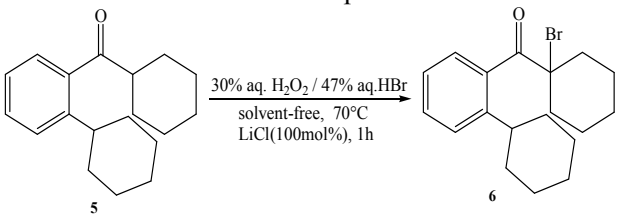
The new reaction condition used for the conversion of **1** to **2** (Table **1**, entry 6), was carried out for the bromination of ketone 3 to obtain the corresponding bromoketone 4. In this case, reaction was completed after 5h at 70 °C and 70% yield was achieved (Table **2**, entry 1). Then, the effect of various catalysts on the bromination reaction was examined. LiCl as a natural catalyst had the best effect on the previous reaction under similar condition. When LiCl was used, the reaction proceeded with 88% conversion in 1h at 70 °C (Table **2**, entry 2). When silica supported sulphuric acid was applied, bromoketone **4** was achieved in 88% yield after 12h at room temperature (Table **2**, entry 5).

Table 2. Bromination of acetophenone with H_2O_2-HBr, under given reaction conditions.



Entry	n(mmol 3:H_2O_2:HBr]	Catalyst (mol %)	Time	Temp	Yield (%)
1	1:2:1.1	-	5	70 °C	70
2	1:2:1.1	LiCl(100)	1	70 °C	88
3	1:1.5:1.1	LiCl(100)	1	70 °C	80
4	1:2:1.1	LiCl(50)	1	70 °C	80
5	1:2:1.1	SiO_2-H_2SO_4 (30wt %)	12	rt	88

Based on the catalytic role of LiCl, the regioselectivity of this reaction under the reaction condition shown in scheme **1** was also evaluated. When ketone **5** was used as a model for bromination under the new conditions, α-position of ketone was brominated and the other CH position remained intact.



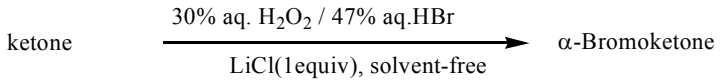
Scheme 1. The bromination reaction condition for ketone **5**

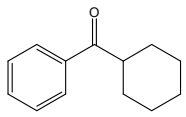
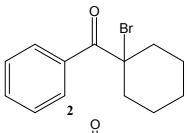
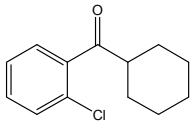
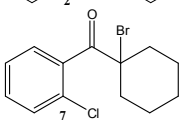
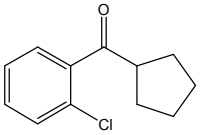
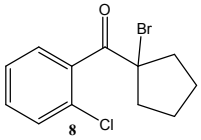
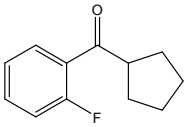
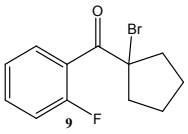
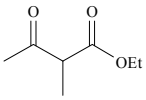
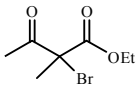
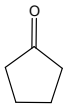
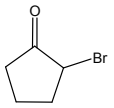
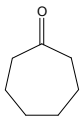
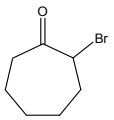
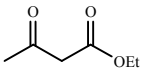
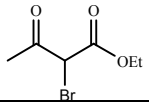
With optimized reaction condition obtained for the conversion of **3** to **4** from the catalyst and reaction temperature point of view, the scope of this transformation was explored. Accordingly, different ketones were examined and high to quantitative yields were noticed in most of the cases.

Conclusion

The effect of various parameters on the bromination reaction of cyclic and acyclic phenyl ketones were examined and was realized that the reaction products and the yields depend on the nature of solvent, temperature, molar ratio of H_2O_2-HBr and LiCl as catalyst. The presented operationally simple and green procedure is a mild, solvent-free and organic waste-free method for the bromination of ketones. It seems to us that the key factor in this procedure is the use of LiCl as a natural catalyst.

Table 3. Bromination of ketones with H_2O_2-HBr catalyzed by LiCl under solvent-free condition.



Entry	Substrate[a]	Time	Temp.	product	Yield%
1		1h	70 °C		98[b]
2		1h	70 °C		97[b, c]
3		1.5h	70 °C		95[b, d]
4		1.5h	70 °C		93[b]
5		10min	rt		97[b]
6		10min	rt		90[e]
7		10min	rt		90[e]
8		10min	rt		87[e]

[a] Ketones that are present in entry 1-4 were synthesized according to the reported procedure.[12]
[b] Isolated yield.
[c] Reaction was completed after 5h at 70 °C without LiCl and 85% yield was obtained.
[d] Bromoketone **8** was used for the synthesis of ketamine.
[e] Conversion was determined using ^{1}H NMR.

Experimental

General remarks

All the reagents were purchased from Merck. IR spectra were recorded on Bruker Tensor 27 and Perkin Elmer. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 250 (250 and 62.5 MHz, respectively) and 300 (300 and 75 MHz, respectively) spectrometer. Chemical shifts were reported on the δ scale relative to TMS. All chemicals were used as-received from the appropriate suppliers.

Synthesis:

*General experimental procedure for the bromination of ketone **1**.*

Ketone **1** (10 mmol) was placed in a flask covered with aluminum foil. An aqueous solution (47%) of HBr (1.2 mL, 1.1 mol equiv.) was added to ketone. After stirring the reaction mixture for 5 min at room temperature, 10 mmol of LiCl was added to the mixture and the mixture was stirred for 1 min. Then, 30% aqueous solution of H_2O_2 (2 mL, 2 mol equiv.) was added slowly. The reaction mixture was heated at 70 ^oC for 1h. Afterward, 5 mL of H_2O was cautiously added, followed by 5 mL of hexane and the mixture was stirred for 5 minutes. The organic layer was separated and dried on $MgSO_4$. The insoluble material was filtered off and then the solvent was evaporated under reduced pressure. The crude reaction mixture was then analyzed by ^1H- and ^{13}C NMR spectroscopy.

*1-Bromocyclohexylphenyl ketone (**2**):*

^1H NMR (250 MHz, $CDCl_3$): δ = 1.33-1.45 (m), 1.48-1.60 (m), 1.72-1.85 (m), 2.12-2.22 (m), 2.28-2.38 (m), 7.37-7.44 (2H, m), 7.48-7.55 (1H, m), 8.04-8.09 (2H, m).; ^{13}C NMR (62.90 MHz, $CDCl_3$), δ: 23.5 (CH_2), 24.9 (CH_2), 38.2 (CH_2), 67.9 (C), 128.1 (2CH), 129.7 (2CH), 132.0 (CH), 135.8 (C), 197.4 (C, C=O).

*1-Bromocyclohexyl-(o-chlorophenyl)-ketone (**7**):*

^1H NMR (250 MHz, $CDCl_3$): δ = 1.60-1.72 (m), 1.75-1.80 (m), 1.90-2.00 (m), 2.18-2.23 (m), 7.28-7.40 (3H, m), 7.80-7.82 (1H, m).; ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.5 ($2CH_2$), 24.8 (CH_2), 36.1 ($2CH_2$), 70.6 (C), 126.3 (CH), 129.0 (CH), 130.0 (CH), 130.3 (C), 130.6 (CH), 137.8 (C), 199.6 (C, C=O).

*1-Bromocyclopentyl-(o-fluorophenyl)-ketone (**9**):*

^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (2H, m), 2.02 (2H, m), 2.37 (4H, m), 7.08-7.21 (2H, m), 7.41-7.48 (1H, m), 7.74-7.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$, *J* in Hz) δ 23.22 (CH_2, s), 40.22 (CH_2, s), 73.81 (C, s), 116 (CH, d, ^2J = 22), 123 (CH, d, ^3J = 3.22), 126 (C, d, ^2J = 14.8), 130 (CH, d, ^4J = 2.3), 132 (CH, d, ^3J = 8.47), 159 (C, d, ^1J = 250.8), 196.37 (C, C=O).

*1-Bromocyclohexyl-(o-cyclohexylphenyl)-ketone (**6**):*

^1H NMR (250 MHz, $CDCl_3$): δ = 1.00-1.30 (m), 1.60-1.80 (m), 1.90-2.00 (m), 2.10-2.20 (m), 7.25-7.42 (3H, m), 7.78-7.82 (1H, dd).; ^{13}C NMR (62.90 MHz, $CDCl_3$), δ: 22.5 (CH_2), 24.8 (CH_2), 26.9 (CH_2), 30.1 (CH_2), 36.1 (CH_2), 43.4 (CH), 70.5 (C), 126.3 (CH), 128.9 (CH), 130.0 (CH), 130.3 (C), 130.5 (CH), 137.8 (C), 199.5 (C, C=O).

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