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Photochemical α-bromination of ketones using *N*-bromosuccinimide: a simple, mild and efficient method

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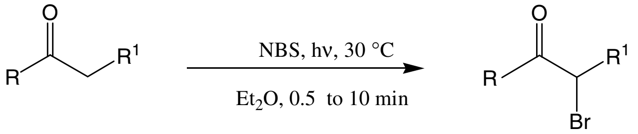
Abstract—Aromatic and aliphatic carbonyl compounds undergo facile bromination with *N*-bromosuccinimide under UV–vis irradiation to give the corresponding α-brominated ketones in good yields, at low temperatures (30 °C), without any catalyst, catalyst support or radical initiator and within a short time.

The α-bromination of carbonyl compounds is an important transformation in synthetic organic chemistry.[1] α-Bromination of the side chain of aromatic ketones has attracted attention because the resulting bromoketones are intermediates for the synthesis of a variety of biologically active compounds.[2] α-Bromination is the first step of introducing a heteroatom so as to provide additional conjugation to the carbonyl group, and for generating stabilized carbon radicals or carbanions. Various α-brominated carbonyl compounds have been synthesized using bromine in the presence of protic and Lewis acids,[3] cupric bromide,[4] dioxane dibromide,[5] *tetra*-butylammonium tribromide[6] and others. The environmentally hazardous bromine has given way to *N*-bromosuccinimide (NBS) as a user friendly reagent and the conditions for bromination have become milder with the advent of suitable catalysts and co-catalysts. The byproduct, succinimide, can be recycled. It has been reported that α-bromination of carbonyl compounds can be carried out by NBS, with radical initiators such as azobisisobutyronitrile[7] (AIBN) and dibenzoyl peroxide[8] (BPO). Das et al.[9] and Tanemura et al.[10] reported that α-bromination using NBS over silica-supported sodium hydrogen sulfate and ammonium acetate leads to good yields of the corresponding ketones. However, this reaction requires high temperatures (~80 °C) and the reaction is slower for the formation of monobromoacyclic ketones. Adhikari and Samant[11] reported sonochemical α-bromination of acetophenones catalyzed by *p*-toluenesulfonic acid using NBS. Recently, Koo and co-workers[12] reported the α-bromination of carbonyl compounds catalyzed by trimethylsilyl trifluoromethanesulfonate in the presence of NBS. Here, we report the photochemical α-bromination of a number of ketones using NBS at room temperature without the use of any catalyst (Scheme 1). Optimization of the reaction conditions for the photochemical α-bromination of carbonyl compounds with NBS was investigated using cyclohexanone as the model substrate (Scheme 2).

The effect of different solvents on the α-bromination of cyclohexanone was studied and the results are summarized in Table 1. The reaction was fast without any catalyst with 86% conversion and a selectivity of 91% for monobromocyclohexanone and 9% for dibromocyclohexanone in diethyl ether (Table 1; entry 1). The conversion of cyclohexanone in different solvents was in the order: $Et_2O > CH_3CN > CCl_4 \sim THF > CH_2Cl_2 \sim DMSO > DMF$, whereas the selectivity towards α-bromocyclohexanone was in the following order: $DMF \sim DMSO > CCl_4 > CH_3CN > Et_2O > CH_2Cl_2 > THF$ (Table 1). Among the solvents used, Et_2O and THF appeared to be the most suitable in terms of the time required for maximum conversion of the cyclohexanone. In all other solvents, the reaction proceeded



Scheme 1.

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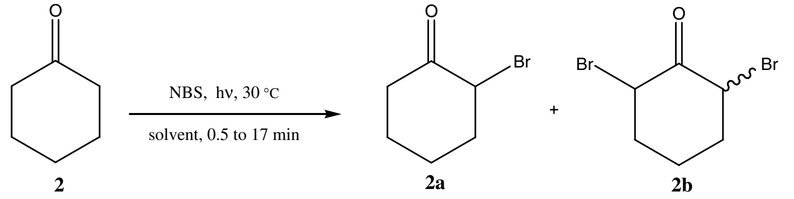


Scheme 2.

Table 1. Effect of solvent on the bromination of cyclohexanone using NBS in the presence of UV–vis irradiation

Entry	Solvent	Time[a] (min)	Conversion wt %	Selectivity %	
				Monobromo-	Dibromo-
1	Et_2O	0.5	86	91	9
2	CH_3CN	17.0	78	95	5
3	CCl_4	10.7	74	97	3
4	THF	0.7	73	77	23
5	CH_2Cl_2	13.5	64	90	10
6	DMSO	7.2	64	98	2
7	DMF	10.5	61	98	2

Reaction conditions: cyclohexanone (1 mmol), NBS (1.05 mmol) and the solvent (5 ml) were stirred under a nitrogen atmosphere and UV–vis irradiation at 30 ± 2 °C. NBS was added in a single portion.

[a] Time taken for maximum conversion of cyclohexanone under the reaction conditions.

rather slowly with the time required for maximum conversion ranging from 7 to 17 min. In general, the selectivity for the monobromo product was higher at lower conversions of the cyclohexanone.

The α-bromination of cyclohexanone with NBS was studied at different temperatures in diethyl ether and the results are shown in Figure 1. The reaction was complete within minutes with α-monobrominated ketone **2a** as the major product and dibrominated ketone **2b** as the minor product. Even at 10 °C, a conversion of 67% and a high selectivity (96%) for **2a** was observed. With an increase in temperature, the conversion increased but the selectivity for **2a** decreased due to bromination of **2a** further to give **2b**. At 35 °C, 89% of cyclohexanone was converted to give 88% of **2a** and 12% of **2b**, respectively.

This reaction using different reagent to substrate mole ratios was studied in Et_2O and the results are shown in Figure 2. From 0.25:1 to 0.75:1 (reagent/substrate) ratios, the conversion increased appreciably while the selectivity for **2a** was 100%. Thereafter, no significant increase in conversion was observed (86–92%). However, the selectivity for **2a** decreased considerably from 91% to 59%, accompanied by an increase in the dibrominated product along with other undesired side products. It was found that for bromination in Et_2O, a mole ratio of 1.05:1 at room temperature (30 ± 2 °C) gave the best yield of **2a**. Under these conditions the reaction was also carried out by adding the NBS in four portions, but there was no difference in conversion or selectivity.

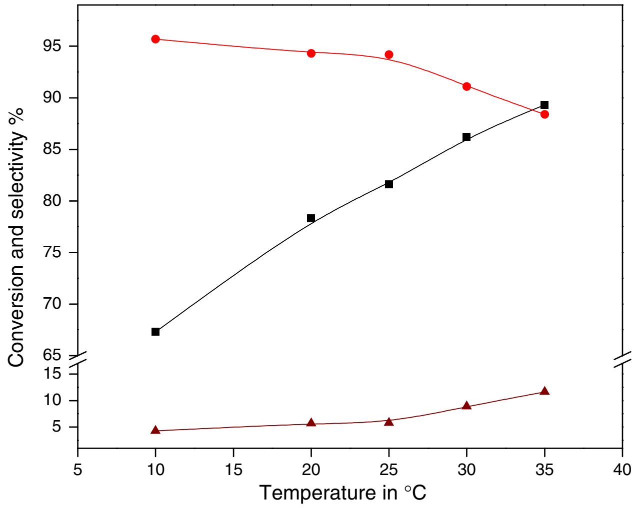


Figure 1. Influence of temperature on the bromination of cyclohexanone and selectivity (%). The reaction between cyclohexanone and NBS in diethyl ether as a solvent was carried out at 30 ± 2 °C under a nitrogen atmosphere and UV–vis irradiation. (■) % Conversion; (●) % selectivity for α-bromocyclohexanone; (▲) % selectivity for dibromocyclohexanone.

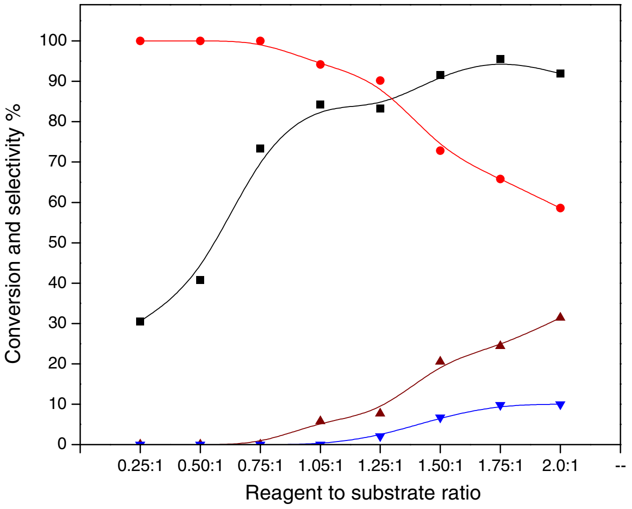
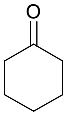
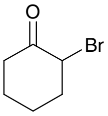
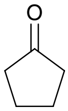
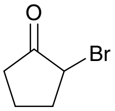
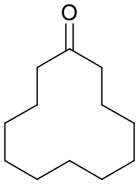
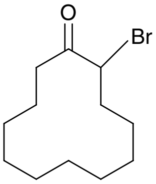
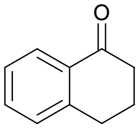
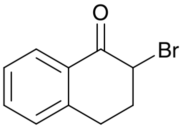
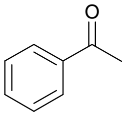
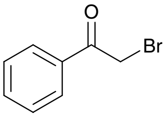
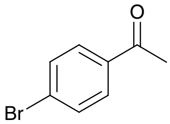
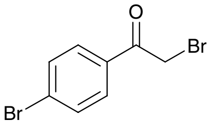
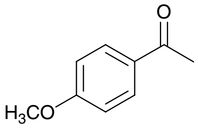
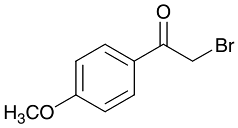
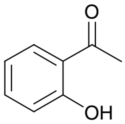
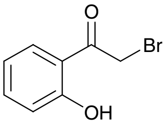
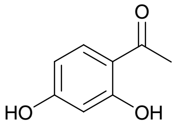
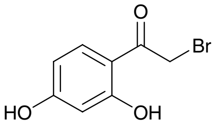
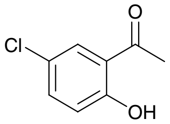
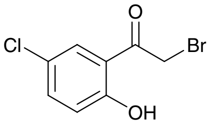
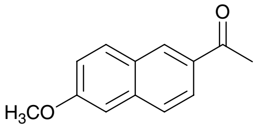
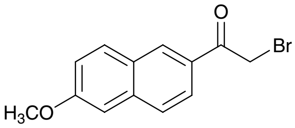


Figure 2. Reagent to substrate ratio versus conversion and selectivity (%) for the reaction between cyclohexanone and NBS in diethyl ether as solvent at 30 ± 2 °C under a nitrogen atmosphere and UV–vis irradiation. (■) % conversion; (●) % selectivity for α-bromocyclohexanone; (▲) % selectivity for dibromocyclohexanone; (▼) % selectivity for other by-products.

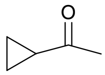
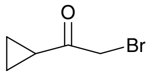
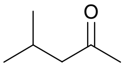
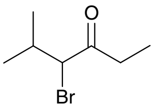
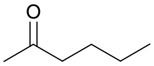
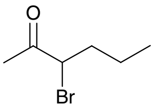
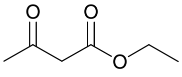
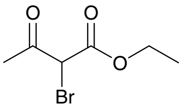
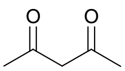
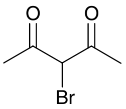
Photochemical α-bromination with NBS was carried out with a number of cyclic as well as acyclic ketones. These substrates were converted at 30 ± 2 °C to the corresponding α-brominated products in excellent yields within a few minutes. The results of these studies are summarized in Table 2. These reactions were carried out with different

Table 2. α-Bromination of cyclic and acyclic ketones with NBS in the presence of UV–vis irradiation

Entry	Substrate	Product	Time (min)	Conversion, wt %		Selectivity[a] %	
				(a)	(a′)	(a)	(a′)
1			0.5	84	94[b]	91	73[b]
2			0.5	62	—	90	—
3			2 0.5	76 —	99 48[b]	100 —	97 97[b]
4			2 0.5	84 43[b]	98 —	100 100[b]	89 —
5			4 1.5	71 35[b]	97 —	100 100[b]	78 —
6			5 1.5	63 23[b]	100 —	100 100[b]	93 —
7			4	67	98	100	85
8			10	15	—	100	—
9			5	75	—	100	—
10			5	41	—	100	—
11			5	67	74	100	94

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Time (min)	Conversion, wt %		Selectivity[a] %	
				(a)	(a′)	(a)	(a′)
12			5	65	93	90	92
13			2	93	98	70	61
14			3	76	100	72	63
15			3	92	—	96	—
16			3	98	—	84	—

Reaction conditions: substrate (1 mmol), NBS (a) 1.05 mmol added in four portions and (a′) 1.5 mmol added in six portions, temperature 30 ± 2 °C, Et_2O 5 ml. The reaction mixture was stirred under a nitrogen atmosphere and UV–vis irradiation.

[a] Selectivity of the corresponding α-bromoketones.

[b] NBS was added in one portion.

equivalents of NBS (1.05 and 1.5 mmol). It was observed that the conversion of the ketones increased with additional moles of NBS. However, the stepwise addition of NBS to the reaction mixture generally led to a higher conversion of the substrate and a higher selectivity for the monobrominated product. Usually portion-wise addition required a longer reaction time than for a single addition (entries 3–6). This may be due to controlled formation and release of Br free radicals that react with the substrate molecules at a steady rate, thereby increasing the conversion of the substrate as well as the selectivity to monobromoketones and eliminating unwanted side products. The bromination of cyclopentanone gave 62% conversion with 90% selectivity (entry 2). The conversion decreased with the ring size of the cyclic ketones (entries 1 and 2); however, there was no change in selectivity. Cyclododecanone (entry 3) showed 76% and 99% conversion with 100% and 97% selectivity for α-bromocyclododecanone using 1.05 and 1.5 equiv of NBS, respectively. For tetralone and acetophenone, the addition of NBS in a single portion (entries 4 and 5) gave conversions of 43% and 35%, respectively, with 100% selectivity for the respective monobromoketones. However, the conversion of tetralone and acetophenone increased to 84% and 71% with 100% selectivity for monobromo products by the addition of NBS in four portions. Aromatic ketones gave only monobrominated products (entries 5–11). As compared to *para*-substituted acetophenones, *ortho*-substituted acetophenones showed lower conversions to the respective α-monobromoketones. Unsymmetric acyclic ketones also afforded two products derived from bromination at the two α-positions (entries 13 and 15). When 1.5 equiv of NBS was used, a mixture of the two α-monobromo products was observed. These reactions were also carried out under irradiation using sunlight. Similar conversions and selectivity were recorded, indicating the general nature of the photoinitiated bromination.

The mechanism is believed to follow a radical pathway.[13] This was verified by the addition of the reaction mixture to 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution prepared in ethanol and recording the UV–vis spectrum.[14] A blue shift in the absorption wavelength, from λ_{max} at 517 nm for DPPH in ethanol to 385 nm for DPPH and the reaction mixture in ethanol (Fig. 3) confirmed the formation of free radicals in this reaction.

In conclusion, we have demonstrated a simple, photochemical reaction procedure for the effective bromination of ketones with NBS, which within a short reaction time gives high conversions of ketones and very high selectivity for the α-monobrominated products.

General experimental procedure: A mixture of the ketone (1 mmol) and NBS (1.05–1.5 mmol) was stirred under a nitrogen atmosphere in 5 ml of diethyl ether in a two-neck round bottom flask under a Philips HPL-N (250 W, $\lambda = 200$–600 nm) lamp fitted with a water circulation arrangement at room temperature (30 ± 2 °C). In order to achieve the best yield of the product, NBS was added in four portions, each portion containing 0.25 equiv. The reaction product was filtered, diluted with diethyl ether and washed with water. The organic

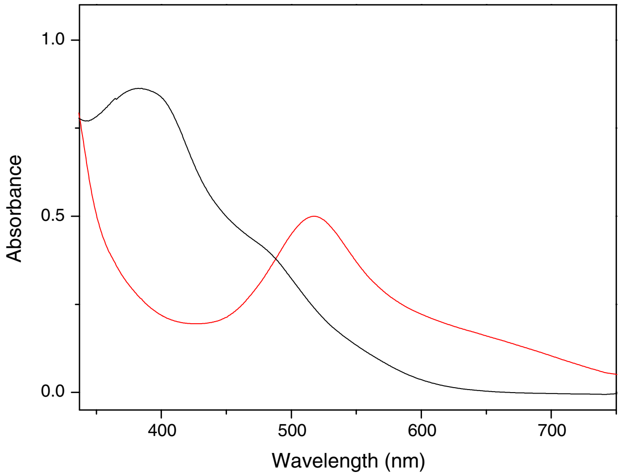


Figure 3. UV–vis absorption spectra of (—) DPPH in ethanol and (—) reaction mixture in DPPH.

layer was separated and dried over sodium sulfate. The product was analyzed by GC (HP 5890) using a capillary column (HP-5). GC mass spectra were taken on a Shimadzu GC–MS-QP5050A spectrometer equipped with a DB-5 column to identify the products.

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