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Oxidations with IBX: benzyl halides to carbonyl compounds, and the one-pot conversion of olefins to 1,2-diketones

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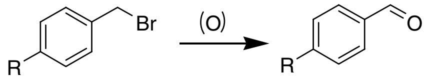
Abstract—A variety of benzyl halides were converted to the corresponding aldehydes/ketones in respectable yields by IBX in DMSO at 65 °C. The bromohydrin reaction of olefins using NBS–H_2O in DMSO can be nicely adapted to IBX-mediated oxidation of benzyl halides in such a way that olefins are converted to the corresponding 1,2-diketones in good isolated yields in one-pot.

The oxidation of halides to the corresponding carbonyl compounds constitutes an important transformation in synthetic organic chemistry (Eq. 1). The oldest method for such a conversion constitutes the Hass–Bender reaction,[1] which involves O-alkylation of the nitronate anion followed by decomposition of the resulting intermediate. The Sommelet reaction[2] is another well-known reaction to effect this transformation, and involves the use of hexamethylenetetramine to afford the formaldehyde imine derivative of the primary amine, which tautomerises to the methyl imine of the desired carbonyl compound. While the former method requires a strong base, the latter unfortunately has limited substrate scope. Other notable methods to accomplish this conversion include the Krohnke reaction,[3] the Kornblum reaction,[4] and a number of its variants,[5] the use of *N*-alkoxypyridinium salts,[6] potassium chromate,[7] $NaIO_4$–DMF,[8] oxodiperoxovanadate,[9] etc.[10] All of these procedures, however, are invariably associated with certain limitations in terms of acid/base conditions, long reaction times, poor yields, substrate scope, high temperature, etc.



(1)

In continuation of our recent studies with IBX (*o*-iodoxybenzoic acid),[11,12] we conceived the possibility of converting halides to the corresponding carbonyl compounds in a simple fashion. Herein, we report that IBX in DMSO can be conveniently utilized to accomplish the conversion of benzylic halides to the corresponding aldehydes/ketones in respectable yields under mild reaction conditions. Further, we demonstrate that this methodology can be conveniently combined with the bromohydrin reaction of olefins (NBS–H_2O) in DMSO[13] to access 1,2-diketones in one pot.

Oxidation of benzyl halides: In our initial experiments, we observed that the reaction of benzyl halides with IBX in DMSO occurred rather slowly at room temperature, while that of aliphatic halides did not proceed at all. To maximize the yields, the reaction conditions were optimized with *p*-bromobenzyl bromide as a representative case. Thus, when the reactions were run in DMSO in the presence of 2–3 equiv of IBX at a slightly elevated temperature,[14] that is, at 60–70 °C, a variety of benzyl halides were found to undergo conversion to their corresponding aldehydes/ketones (Table 1); the use of both freshly distilled and rigorously dried (distilled over CaH_2) DMSO yielded similar results. Notably, aliphatic bromides, for example, octyl bromide, were found to be unreactive even after 14 h at a temperature of 65 °C (Table 1, entry 11). A perusal of the results in Table 1 reveals that cinnamyl bromide as well as sterically hindered mesityl bromide (entries 5 and 6) undergoes smooth conversion to the corresponding aldehyde in reasonable yields. Indeed, a dibromide such as acenaphthylene dibromide could be readily converted to the corresponding diketone (entry 9). In a similar manner, bromohydrin was conveniently converted to

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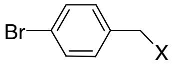
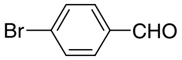
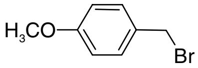
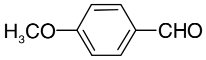
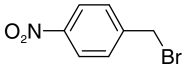
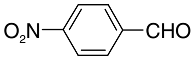
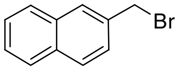
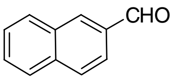
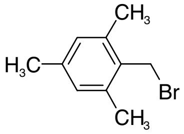
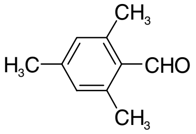
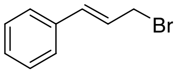
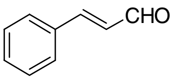
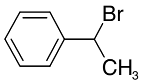
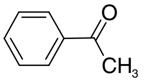
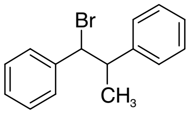
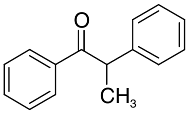
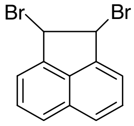
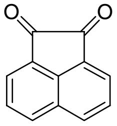
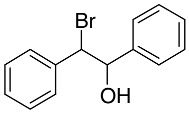
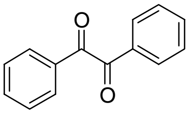
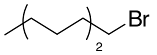
Table 1. Results of the IBX-mediated conversion of halides to carbonyl compounds

Entry	Substrate	IBX (equiv)	Temp (°C)	Time (h)	Product	Yield (%)
1						
	X = Br	3.0	65	1.5		70
	X = Br	1.2	65	5.0		60
	X = Br	0.5	65	12.0		30
	X = Cl	1.5	65	14.0		30[a]
	X = I	1.5	25	1.5		90
2		1.5	40	0.5		65
		2.0	25	0.5		77
3		2.5	65	8.0		73
4		1.5	65	5.0		66
5		1.6	65	2.5		80
6		1.5	65	2.5		62
7		1.5	65	7.5		64
8		1.5	65	10.0		65
9		2.5	65	4.0		50[b]
10		3.0	65	4.0		83
11		1.5	65	14.0	—[c]	

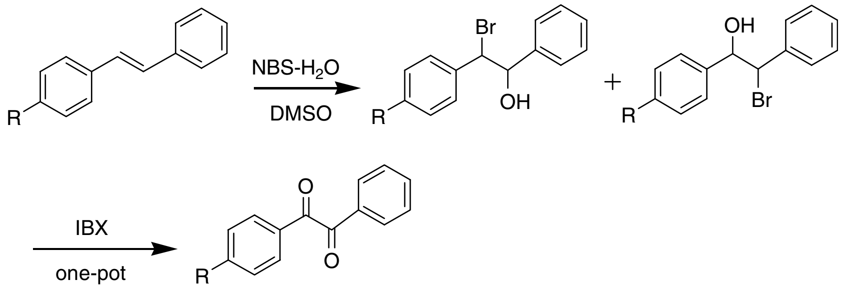
[a] Conversion is 78%.

[b] Conversion is 65%.

[c] No reaction.

the diketone (entry 10). The dependence of the reaction on the nature of the halogen was examined with *p*-bromobenzyl derivatives. Whereas the reaction was found to be quite fast and also yielded the aldehyde in 90% yield when the halide was iodide, the reaction of the chloro-derivative was found to be sluggish with a conversion of 78% leading to a 30% isolated yield of the aldehyde. The benzyl bromides reacted with a reasonable rate as reflected from the reaction times and yielded the aldehydes in 60–70%. The experiments with *p*-bromobenzyl bromide revealed that the reaction progresses rapidly and in better yields when IBX was employed in large excess (Table 1, entry 1).

One-pot transformations: We envisaged that the IBX-mediated conversion of benzyl halides to the carbonyl compounds could be readily adapted to one-pot transformations by capitalizing on the well-documented NBS–H_2O-mediated conversion of olefins in DMSO to the corresponding bromohydrins, which can be oxidized with IBX to dicarbonyl compounds according to Eq. 2.

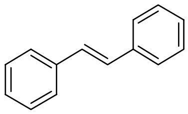
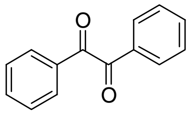
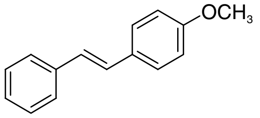
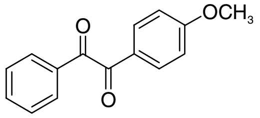
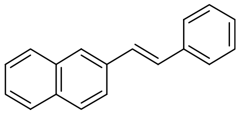
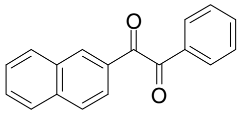
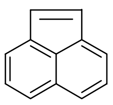
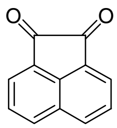


(2)

Thus, the diaryl-substituted olefins were converted to bromohydrins with NBS–H_2O in DMSO, and the latter were subjected to oxidation by introducing IBX into the same pot.[15] Stilbene afforded benzil in 50% isolated yield in a one-pot conversion, although the same product was obtained in an overall yield of 71% via a step-wise protocol (Table 2, entry 1). The yields were found to be significantly higher for *p*-methoxystilbene and 2-styrylnaphthalene (entries 2 and 3). The one-pot conversion of acenaphthylene yielded the corresponding diketone in 79% isolated yield (entry 4). Clearly, the facile conversion of benzyl halides with IBX in DMSO can be advantageously utilized to accomplish one-pot reactions as revealed from the results in Table 2.

Mechanistic rationalizations: *p*-Nitrobenzyl bromide is known to react when stirred in DMSO at room temperature to yield the corresponding aldehyde in 48% yield.[4a] The same reaction, however, does not work satisfactorily for a broad range of benzyl halides. In view of this, we monitored the progress of the reaction for two representative halides, that is, *p*-nitrobenzyl bromide and *p*-methoxybenzyl bromide, by ^{1}H NMR spectroscopy. The NMR scans for the progress of the reaction for *p*-nitrobenzyl bromide (at 65 °C) and *p*-methoxybenzyl bromide (at 30 °C) are shown in Figure 1. In the case of *p*-nitrobenzyl bromide, the reaction went almost to completion (> 90%) in 3 h in the presence of 2 equiv of IBX, while the formation of aldehyde was virtually imperceptible without the added IBX (Fig. 1, bottom scans). This clearly shows the role of IBX in the conversion of the benzyl halide to the corresponding aldehyde. A similar monitoring of the reaction of *p*-methoxybenzyl bromide in DMSO without added IBX revealed that it slowly reacted with the solvent to produce new signals in ^{1}H NMR at ca. δ 5.4 and 7.0 (Fig. 1, top scans a and b), which could be ascribed to the formation of a salt resulting from the attack of DMSO on the benzyl halide (cf. Scheme 1). Although the yield of the salt increases progressively, its decomposition to the aldehyde did not occur until after 2 h as revealed by the ^{1}H NMR. In contrast, introduction of IBX led to a rapid reaction with a gradual disappearance of the signals attributable to the starting compound as well as the salt with concomitant appearance of the signals of the aldehyde (cf. Fig. 1, top scans c and d). The formation of aldehyde

Table 2. Results of the one-pot conversion of olefins to 1,2-diketones using NBS-DMSO:H_2O and IBX

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		5.0		50 (71)[b]
2		3.0		65
3		3.5		67
4		3.0		79

[a] Isolated yields based on reactions carried out on 1 mmol scale.

[b] Overall yield based on a stepwise protocol.

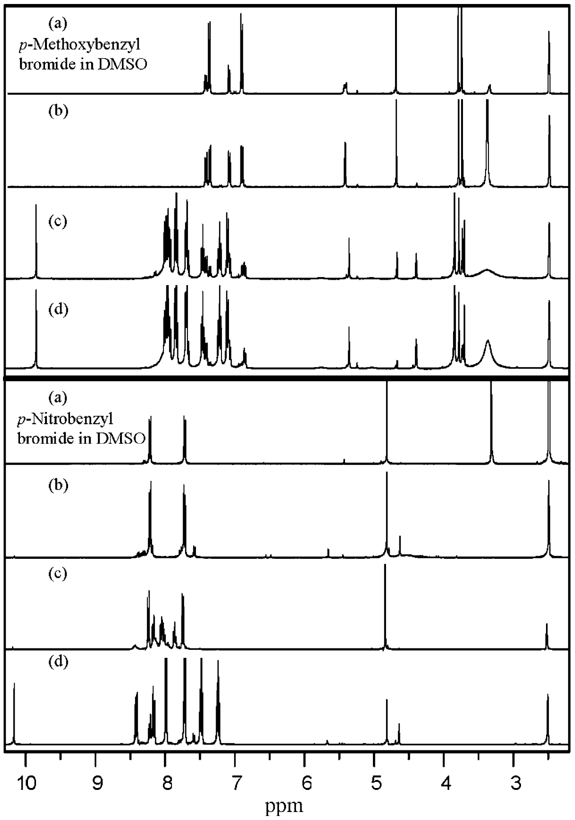
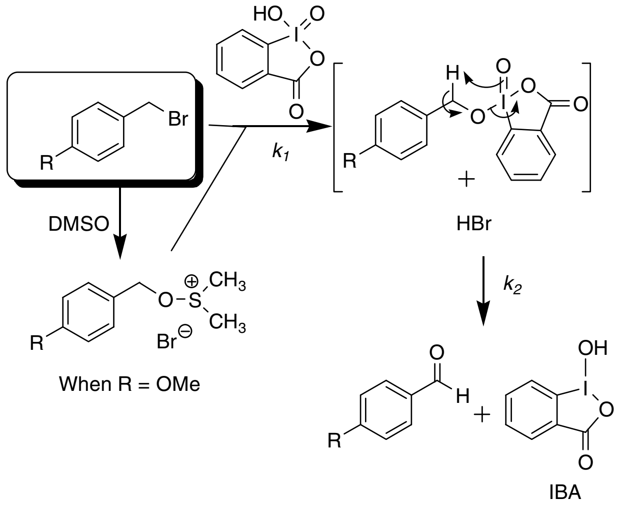


Figure 1. ^{1}H NMR monitoring of the reactions of *p*-methoxybenzyl bromide and *p*-nitrobenzyl bromide in DMSO-d_6. Top: (a) without IBX/5 min/rt, (b) without IBX/2 h/rt, (c) with IBX (2 equiv)/5 min/rt, and (d) with IBX (2 equiv)/30 min/rt. Bottom: (a) without IBX/5 min/rt, (b) without IBX/2 h/65 °C, (c) with IBX (2 equiv)/5 min/rt, and (d) with IBX (2 equiv)/2 h/65 °C.



Scheme 1. Mechanism for the oxidation of benzyl halides to carbonyl compounds.

could be recognized readily within 5 min of introducing IBX. It is noteworthy that the formation of the aldehyde is accompanied by a small amount of the alcohol in both cases as revealed by the ^{1}H NMR signals of the diagnostic benzylic protons at ca. δ 4.4 and 4.6 for *p*-methoxybenzyl alcohol and *p*-nitrobenzyl alcohol, respectively. While the formation of the alcohol is not readily explicable,[16] the mechanism of conversion of benzyl halides to the corresponding carbonyl compounds via initial formation of alcohol and its subsequent oxidation with IBX is ruled out by a comparison of the ^{1}H NMR scans of the benzyl halides in DMSO after 2 h with and without the added IBX (cf. Fig. 1). Based on these considerations, the mechanism of formation of the carbonyl derivative may be depicted as shown in Scheme 1. Accordingly, the reaction of benzyl bromide may lead to the addition product, presumably via the salt in the case of electron-rich benzyl halides such as *p*-methoxybenzyl bromide. While an S_N1 mechanism presumably applies for electron rich halides, an S_N2 mechanism may operate for electron-deficient cases. The addition product may subsequently decompose to the aldehyde with liberation of iodosobenzoic acid (IBA). Accordingly, while the formation of adduct (k_1) may be rate determining in the case of electron deficient halides, decomposition may become rate determining in the case of electron rich benzyl halides (k_2).

In accordance with the mechanism in Scheme 1, only 1 equiv of IBX should suffice for the oxidation of benzyl halides. Quite inexplicably though (i) excess IBX afforded higher yields of the carbonyl products, and (ii) benzyl chlorides were found to react only sluggishly leading to low isolated yields. Careful monitoring of the reaction shows that the initially generated HX is quite detrimental to IBX in DMSO. In a control experiment, we found that IBX is reduced to *o*-iodobenzoic acid in HBr-saturated DMSO. Thus, a consequence of the slow reaction of IBX with the benzyl halide (e.g., benzyl chloride) is that the initially generated HX entirely destroys the IBX in a catalytic manner, such that the halides cannot be completely converted to the carbonyl compound. A further complication is that the *o*-iodosobenzoic acid, the partial reduction product of IBX, may compete with the benzyl halide to afford undesirable ethers. Thus, the reaction can be facilitated with a large excess of IBX. The conversion works extremely well when the halide is iodide due to a faster reaction rate, which obviates the reduction of IBX by the in situ generated HX.

In summary, we have shown that IBX can be conveniently employed in DMSO as a solvent for the conversion of benzyl halides to the corresponding carbonyl compounds in respectable isolated yields. While the reaction does not work at all for aliphatic halides and proceeds only sluggishly for benzyl chlorides, the carbonyl compounds can be obtained in moderate to excellent isolated yields when the halide is bromide or iodide. This transformation can be conveniently adapted to the one-pot conversion of olefins to 1,2-diketones via the formation of bromohydrins using NBS–H_2O. Given that IBX is *cheap* and is becoming an increasingly popular oxidation reagent due to its *environmentally benign attributes*,[12] the conversion of benzyl halides to the carbonyl compounds reported herein constitutes an invaluable addition to the repertoire of transformations mediated by IBX.

Acknowledgements

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14. General procedure for the conversion of benzyl halides to carbonyl compounds: In a typical experiment, 1–2 mmol of the halide and 1.5–2.0 equiv of IBX in 1.0 mL of DMSO were heated at 60–70 °C under a N_2 atmosphere. After completion of the reaction as determined by TLC analysis, the reaction mixture was quenched with water and the organic matter was extracted with ethyl acetate. Silica gel chromatography of the crude mixture yielded the products, which were characterized spectroscopically.
15. General procedure for the one-pot conversion of olefins to 1,2-diketones: The olefin (1–2 mmol) in 1.0 mL of DMSO was treated with 2.0 equiv each of water and NBS under a N_2 atmosphere. The progress of the reaction was monitored by TLC analysis. As soon as the starting material disappeared, 3.0 equiv of IBX was introduced into the same pot and the reaction mixture was heated at 60–70 °C. After completion of the reaction, it was quenched with water and extracted with ethyl acetate. The products were purified by silica gel chromatography and characterized spectroscopically.
16. The formation of alcohol was observed, as monitored from GC analysis, regardless of whether the reaction was run in freshly distilled DMSO or rigorously dried DMSO. By employing more equivalents of IBX, the yields of the oxidation products could be improved in addition to reducing the reaction time (cf. Table 1, entry 1).