Tetrahedron Letters 50 (2009) 2493–2496

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An expedient protocol for conversion of olefins to α-bromo/iodoketones using IBX and NBS/NIS

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ARTICLE INFO

Article history:
Received 30 January 2009
Revised 5 March 2009
Accepted 6 March 2009
Available online 13 March 2009

ABSTRACT

A variety of olefins have been shown to undergo conversion to the corresponding α-bromo/iodoketones when reacted with NBS/NIS and IBX in DMSO at room temperature. While the reaction is found to occur rapidly with e-rich arylolefins leading to the corresponding haloketones in 65–95% yields in 0.3–3.0 h, those containing e-withdrawing groups are found to yield diketones concomitantly, such that the latter are the exclusive products over extended duration of the reactions.

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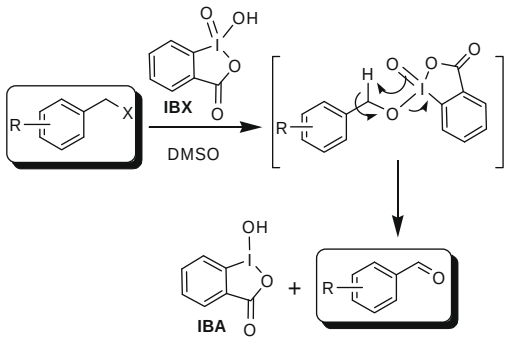
α-Haloketones are indispensable intermediates in organic synthesis. They are conveniently converted to a number of important compounds. For example, they are transformed into (i) aldols stereospecifically in the presence of Cr(II) salts,[1] (ii) α-allyl carbonyl compounds by reacting with allyl gallium/indium reagents,[2] (iii) arylacetic acids through Ag-assisted rearrangement of the primary or secondary α-bromo-alkylarylketones,[3] and (iv) β-diketones using $EtZnCH_2I$.[4] They are exploited in the conversion of vinylsilanes to ketones,[5] γ-allylation of α,β-unsaturated amides,[6] etc.

In general, α-haloketones are prepared from ketones or olefins. Insofar as the synthesis of α-bromoketones from ketones is concerned, a variety of procedures have been reported in addition to the protocol involving the reaction of ketones directly with Br_2 in AcOH.[7] For example, α-bromoketones have been prepared by the reaction of ketones with (i) silica gel-supported dioxane-dibromide under microwave irradiation conditions,[8] (ii) [hydroxy(tosyloxy)iodo]benzene (HTIB) followed by $MgBr_2$ under microwave irradiation,[9] (iii) *N*-methylpyrrolidin-2-one hydrotribromide (MPHT),[10] (iv) $CuBr_2$ in ethyl acetate at reflux conditions,[11] etc. They have also been prepared by employing NBS in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-OTf).[12] In a similar manner, a number of synthetic procedures are known for direct conversion of ketones to their corresponding α-iodoketones, which include the reaction of ketones with molecular iodine directly[13a] or in combination with an additional reagent, for example, I_2–ceric ammonium nitrate (CAN),[13b] I_2–$HgCl_2$,[14] I_2–SeO_2,[15] I_2/urea/H_2O_2,[16] I_2–trimethylorthoformate,[17] etc. As in the synthesis of α-bromoketones, NIS has also been employed together with PTS for the conversion of ketones to their α-halo derivatives.[18]

In general, direct conversion of olefins to α-bromo/iodoketones is synthetically advantageous than that involving ketones. Besides, the fact that the olefins are less expensive than ketones renders the protocol involving olefin conversion cost effective. Incidentally, the number of procedures known for the conversion of olefins to α-bromo/iodoketones is rather limited; α-iodoketones have been synthesized by the reaction of olefins with I_2/silver chromate,[19] I_2/pyridinium dichromate/molecular sieves,[20] and $I^+(collidine)_2BF_4^-$/DMSO.[21] Arylolefins such as styrenes have been converted to α-iodoacetophenones by UV irradiation in the presence of molecular iodine and oxygen.[22] We are aware of only two procedures for the preparation of α-bromoketones directly from olefins; treatment of olefins with sodium bromite in acetic acid has been reported to afford α-bromoketones.[23] Vanadium-catalyzed bromination of olefins has been reported to afford α-bromoketones, but in very less yield.[24] A common procedure that leads to both α-bromo and iodocarbonyl compounds is still scarce.

In our continuing investigations on synthetic transformations mediated by IBX,[25] we recently reported that benzyl bromides can be conveniently transformed into benzaldehydes by reacting with IBX in DMSO.[25c] Mechanistically, we suggested that benzyl bromides might undergo nucleophilic substitution with IBX



Scheme 1.

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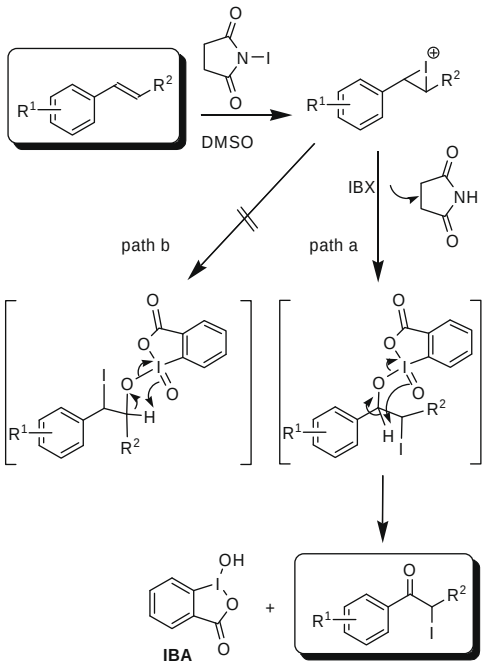
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.032



Scheme 2.

leading to monoalkoxyperiodinane, which collapses to the aldehyde and iodosobenzoic acid (IBA) (Scheme 1). In extension of these studies, we envisaged that the halonium species derived from the reaction of olefins with NBS/NIS could be attacked by IBX, as shown in Scheme 2, leading to alkoxyperiodinanes, which collapse to α-halocarbonyl compounds. Herein, we report that the olefins do undergo consecutive halogenation and oxidation reactions to afford α-halocarbonyl compounds in excellent isolated yields.

In our initial experiments with 2-methylstyrene, the reaction was conducted in DMSO at room temperature with 1.1 and 1.0–1.5 equiv of NBS/NIS and IBX, respectively. While the formation of 2-halopropiophenone was readily observed, incomplete conversion of the olefin was noted even after 1–2 h of the reaction. Extended reaction times to ensure complete conversion of the starting olefin were found to lead to the slow formation of the diketone, which was reasoned to arise as a result of Kornblum oxidation mediated by the DMSO solvent.[26] The use of excess IBX was found to minimize the formation of the diketone product and yield α-halocarbonyl compound quantitatively. Evidently, the excess IBX reagent leads to rapid conversion of the olefin, whereby rather slow formation of diketone product is minimized. Thus, by employing 2.0 equiv of IBX and 1.1 equiv of NBS/NIS, the conversion of a variety of olefins to the corresponding α-halocarbonyl compounds was investigated.[27] The results of consecutive halogenation and oxidation reactions of olefins with NBS/NIS and IBX in DMSO are given in Table 1.

Table 1
Results of conversion of olefins to the corresponding α-bromo/iodoketones with IBX and NBS/NIS[a]

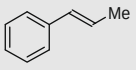
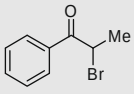
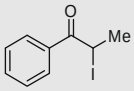
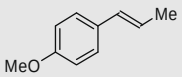
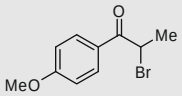
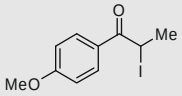
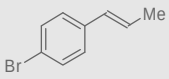
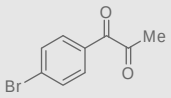
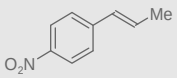
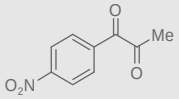
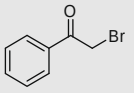
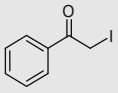
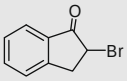
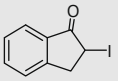
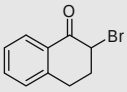
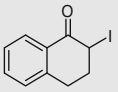
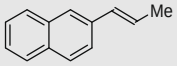
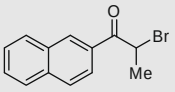
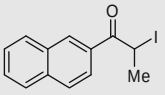
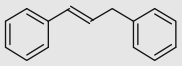
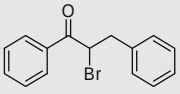
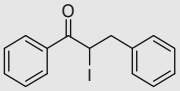
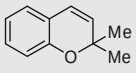
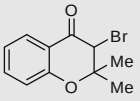
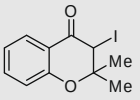
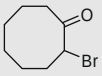
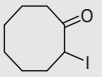
Entry	Substrate	Reagent	Time (h)	Product	Yield (%)
1		NBS	1.1		83
2		NIS	0.7		84
3		NBS	0.3		92
4		NIS	0.2		70[b]
5		NBS	4.0		84[c]
6		NBS	2.5		61[c]
7		NBS	0.4		88
8		NIS	0.3		95

Table 1 (*continued*)

Entry	Substrate	Reagent	Time (h)	Product	Yield (%)
9		NBS	3.0		79
10		NIS	3.0		69
11		NBS	1.0		93
12		NIS	3.0		84
13		NBS	1.0		91
14		NIS	1.0		76[d]
15		NBS	3.0		88[e]
16		NIS	2.5		90
17		NBS	0.5		88
18		NIS	1.5		86
19		NBS	3.0		72
20		NIS	1.5		83
21		NBS	0.5		65[f]
22		NIS	0.5		82

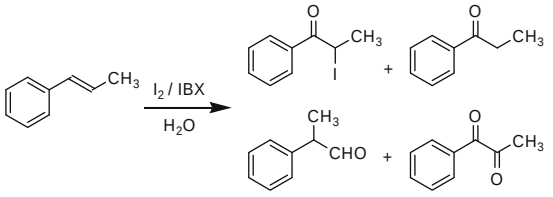
[a] All the reactions were conducted on 1–2 mmol of olefin at room temperature (25–35 °C) by employing 1.1 and 2.0 equiv of NBS/NIS and IBX, respectively.
[b] From ^{1}H NMR analysis of the reaction mixture, a rearranged aldehyde (cf. Eq. 1) was found to be formed in ca. 25%.
[c] The reaction was run at 60–65 °C to ensure complete conversion of the olefin.
[d] The diketone product was isolated in 10% yield.
[e] Conversion was 67%.
[f] Conversion was 83%.

As can be seen in Table 1, a variety of olefins, with the exception of *p*-bromo- and *p*-nitro-2-methylstyrenes (entries 5 and 6), react with NBS/NIS and IBX at room temperature to yield α-bromo/iodoketones in 65–95% isolated yields; for the bromo- and

nitro-substituted 2-methylstyrenes, the diketone was found to be formed concomitantly with the formation of α-haloketones (entries 5 and 6). A similar scenario was observed for their reaction with NIS as well. Thus, the reaction in these cases was run at 60–65 °C until the initially formed α-haloketone was converted to the diketone. Evidently, the e-withdrawing substituents remarkably modify the reactivity of α-haloketones with DMSO. It is noteworthy that Kornblum oxidation involving benzyl halides to aldehydes and phenacyl halides to phenylglyoxals occurs with activated cases. Indeed, it is known that the rate of Kornblum oxidation of α-bromo aromatic ketones to glyoxals is controlled by the substituents.[26] Otherwise, a comparison of the results of 2-methylstyrene with those of the *p*-methoxy-substituted derivative (entries 1–4) suggests that e-rich olefins lead to haloketones quite rapidly and in excellent isolated yields.

The reactions of 2-methylstyrene and cyclohexene with NIS/IBX in DMSO-d_6 were monitored directly by ^{1}H NMR spectroscopy. In particular, the formation of regioisomeric haloketone, cf. path b, Scheme 2, was found to be completely absent in the case of 2-methylstyrene. In a similar manner, for all the aryl or alkyl olefins, the crude product mixtures were analyzed by ^{1}H NMR to establish the lack of formation of the regioisomeric product.

While our investigations were in progress, Yadav et al. reported that olefins as well as terminal alkynes can be converted to α-haloketones with I_2/IBX in water.[28] While this protocol is applicable only to the preparation of α-iodoketones, we have found that the procedure is of limited substrate-scope in that it does not work well for olefins that are substituted. For example, the reaction of 2-methylstyrene under the reported conditions of the reaction, that is, I_2 (1.0 equiv)/IBX (1.2 equiv)/H_2O, rt, 4 h, was found to lead to as many as four products as revealed by ^{1}H NMR spectroscopy (Eq. 1). In contrast, the procedure disclosed herein is not only convenient, but also enables the accessibility of both α-bromo and iodoketones in high yields with a common procedure.



(1)

Although IBX was discovered a century ago, its true potential in accomplishing diverse synthetic transformations has begun to be explored only in recent times. The facile conversion of olefins to haloketones reported herein, albeit limited to e-rich olefins, will undoubtedly expand the ambit of synthetic transformations mediated by IBX.

Acknowledgments

J.N.M. is thankful to the Department of Science and Technology (DST), India for financial support. K.S. is grateful to UGC for a senior research fellowship.

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27. *Representative procedure*: To a clear solution of IBX (2 mmol) in 2–3 mL of DMSO was added the olefin (1 mmol) followed by NXS (1.1 mmol). The reaction mixture was stirred for the duration mentioned in Table 1. Subsequently, the reaction was poured into water and extracted with chloroform. After the usual work-up, the product was isolated by rapid silica-gel column chromatography.
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