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A new method for the synthesis of *Z*-enediones *via* IBX-mediated oxidative rearrangement of 2-alkynyl alcohol systems†

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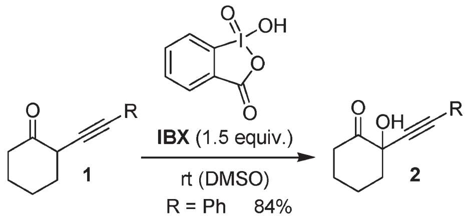
***o*-Iodoxybenzoic acid (IBX) was found to mediate the conversion of α-alkynyl alcohols into *Z*-enediones under notably mild conditions *via* a novel rearrangement mechanism (33–65% yield, 13 examples).**

Within the past decade, IBX (*o*-iodoxybenzoic acid)[1] has emerged as a powerful oxidant for several oxidative transformations.[2–5] Recently, IBX has been shown to enable conversions which proceed *via* oxygen transfer and expulsion of iodosobenzoic acid (IBA) using the oxide ligand of IBX as a nucleophile.[5,6] During our ongoing investigation of oxygenation reactions using polyvalent iodine compounds,[7] we found that IBX is an excellent reagent for the α-hydroxylation of α-alkynyl carbonyl compounds without giving dehydrogenation products.[8] For example, reaction of cyclic ketone **1** with 1.5 equiv. of IBX in DMSO at room temperature produced the tertiary alcohol **2** in good yield (84%) and regioselectivity (eqn. 1). This transformation is of particular importance as tertiary alcohols are formed in high yields with R being silyl, alkyl and aryl substituents.



(1)

We anticipated that IBX may also oxidize α-alkynyl carbonyl compounds which do not possess further substituents in the α-position. Oxidation of 2-alkynyl alcohols **3** should give access to 1,2-diketo compounds **4** (Fig. 1). Unfortunately, treatment of alcohols **3** with an excess of IBX to give the desired diketones **4** was typically not high-yielding, forming instead the allenyl ketones **5** (with R = alkyl) and the *Z*-configured enediones **6** (with R = aryl, alkenyl) as main products. We disclose herein a novel IBX-mediated reaction that allows for the synthesis of *Z*-enediones through an unprecedented oxidative rearrangement mechanism.

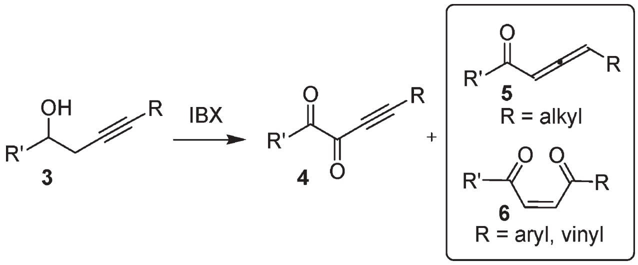


Fig. 1 IBX-mediated oxidation of 2-alkynyl alcohols **3**.

The starting materials for the oxidations are the 2-alkynyl alcohols **3**, which are available on a multigram scale from the corresponding oxiranes and lithium acetylides in high yields (70–92%) using a procedure originally reported by Yamaguchi and coworkers [Li–C≡C–R (1 equiv.), $BF_3 \cdot OEt_2$ (1 equiv.), −78 °C, THF].[9] Oxidations of alkynyl alcohols **3** in the presence of IBX were examined initially under reaction conditions employed previously[8] for the α-hydroxylation of ketone **1**. Under these conditions, reaction of the alkyl substituted alkyne **3a** [R′ = Et, R = $(CH_2)_3$OTHP] with 3.0 equiv. of IBX gave allenyl ketone **5a** as sole product in 75% yield with 11% recovered **3a** after 12 h (Table 1, entry 1). The reaction of further substrates with R being alkyl showed that the formation of allenyl ketones **5** is predominant using IBX in DMSO for the oxidation of 2-alkynyl alcohols **3**. These results indicated that oxidation of alcohol **3a** provided the corresponding ketone, which is then further isomerized to allenone **5a** without undergoing the anticipated oxidation in the α-position.

Table 1 Formation of *Z*-enediones **6** from alkynyl alcohols **3**[a]

	3					
Entry	R′	R	#	Time (h)	Yield[b] **5** (%)	Yield[b] **6** (%)
1	Et	$(CH_2)_3$OTHP	**a**	12	75	
2[c]	Et	Ph	**b**	24		65
3	Me	Ph	**c**	18		54
4	*c*-C_6H_{11}	Ph	**d**	24		55
5	AllylOCH$_2$	Ph	**e**	15		43
6[d]	Ph	Ph	**f**	20		59
7	Et	2-Me-phenyl	**g**	15		61
8	Et	4-*t*Bu-phenyl	**h**	20		60
9	Et	2-MeO-phenyl	**i**	15		35
10	Et	4-PhO-phenyl	**j**	18		33
11	Et	4-F-phenyl	**k**	12		52
12	Et	3-thienyl	**l**	17		60
13	Et	1-cyclohexenyl	**m**	18		50
14	Et	2-propenyl	**n**	17		52

[a] Conditions: 1.0 equiv. **3**, 3.0 equiv. IBX, 23 °C, [substrate] = 0.5 M, DMSO. [b] Isolated yield after column chromatography. Facile isomerization on silica is likely responsible for the moderate yield in forming **6**. [c] Diketone **4b** (28%) was isolated. [d] Diketone **4f** (30%) was isolated.

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Interestingly, the reaction of alkynyl alcohol **3b** (R = Ph, R′ = Et) with 3.0 equiv. of IBX in DMSO at room temperature failed to give traces of allenyl ketone **5b**, providing instead *Z*-enedione **6b** as main product in 65% yield after 24 h (entry 2). Increasing the reaction temperature to 60 °C led to the anticipated increase in reaction rate afording **6b** in 49% yield within 1 h, along with a significant amount of unidentified byproducts. In both cases, diketo compound **4b** was formed as major byproduct in 28% and 32% yield, respectively. Treatment of allenyl ketone **5b** with IBX under these conditions did not lead to the formation of *Z*-enedione **6b**, indicating that allenes are unlikely intermediates in the IBX-mediated transformation **3** → **6**. Since IBX is itself a mild acid, we probed the effect of added base or acid. Addition of substoichiometric amounts of *p*-TsOH (0.5 equiv.) tended to favor the formation of diketone **4b** as well as the formation of the *E*-isomer of enedione **6**, while the reaction was slowed markedly when pyridine (1.0 equiv.) was added (55% yield of **6b** after 52 h in the presence of 2 + 3 equiv. of IBX).

As summarized in Table 1,‡ the conversion of **3** to **6** can be accomplished in satisfactory yields under notably practical conditions: substrate concentration of 0.5 M, 3.0 equiv. of IBX, 23 °C, reaction times 12–24 h (entries 2–14).[10] Although not extensively examined at this point, the formation of *Z*-enediones **6** took place with R′ being alkyl and phenyl substituents (entries 2–6). A broad variety of 2-alkynyl alcohols **3** with different aryl and heteroaryl substituents R were effectively converted into the enediones (entries 7–12). The reaction of alkenyl substituted substrates **3m** and **3n** (R = alkenyl) with IBX also took place in moderate yield (entries 13–14). The assignment of *Z* stereochemistry for all compounds **6** was based on the $J_{CH=CH}$ coupling constant of ≈ 12 Hz and was confirmed by NOE studies with **6b**. Under acidic conditions, rapid isomerization to the more stable *E* isomer ($J_{CH=CH} \approx 16$ Hz) occurred.

The method described above provides an easy and flexible entry to *Z*-enediones which are classically prepared by oxidative ring opening of 2,5-disubstituted furans.[11] The synthetic utility of this route is somewhat depreciated by the difficulty in obtaining the furan precursors. Alternatively, approaches using diazo compounds[12] have been suggested to obtain the desired *Z*-enediones.

A plausible mechanism for the IBX-mediated formation of *Z*-enediones reported herein is shown in Fig. 2. Oxidation of alcohol **3** with IBX produces ketone **7**. In the case of R = alkyl, **7** undergoes isomerization to allenyl ketone **5** in the presence of IBX (path A). Since the direct oxygenation at C4 is unlikely, we suggest the formation of intermediate **8**, which undergoes intramolecular oxygen transfer when R is aryl or alkenyl using the oxide ligand of IBX as a nucleophile (path B). Expulsion of iodosobenzoic acid (IBA) and subsequent IBX oxidation then gives diketo compound **4** as a byproduct. As the major pathway, formal [3,3]-sigmatropic rearrangement of intermediate **9** produces allene species **10**, which after proton transfer and loss of IBA gives enedione **6**. This process involves, at some stage, the delivery of a proton to the central carbon of the allene π-system from the sterically less hindered face giving the thermodynamically less stable *Z* alkene with high stereoselectivity.[13]

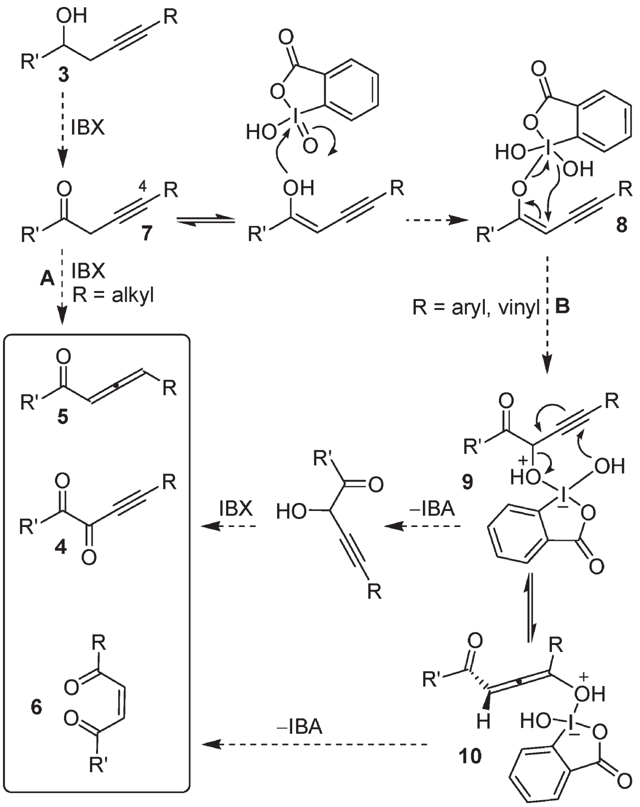

Fig. 2 Possible mechanism for the formation of *Z*-enediones by IBX.

Currently, the experiments are being extended to the synthesis of more complex enediones. As the *Z*-configured enediones should be excellent dienophiles, their cycloaddition chemistry is currently being studied. Possible applications in synthesis will be reported in due course.‡

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Notes and references

‡ *General Procedure*: IBX (0.66 mmol, 184 mg) was added to a solution of alcohol **3** (0.66 mmol) in DMSO (1.3 mL) and the reaction vial was sealed, protected from light and stirred at room temperature. After 30 min, additional IBX (0.66 mmol, 184 mg) was added. After stirring for 1 h at room temperature, a third equivalent of IBX (0.66 mmol, 184 mg) was added. The reaction mixture was then stirred at room temperature for 10–22 h (until TLC analysis indicated complete consumption of starting material and of intermediary occurring ketone **7**), diluted with CH$_2$Cl$_2$ (20 mL), and stirring was continued for 30 min to precipitate the insoluble byproduct, which was removed by filtration. The precipitate was washed with CH$_2$Cl$_2$ (2 × 5 mL), and the combined filtrate was subsequently diluted with water (20 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic phases were washed with brine (30 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica to afford the corresponding *Z*-enediones **6** in 33–65% yield.

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