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Oxidation of *N,N*-Disubstituted Hydroxylamines to Nitrones with Hypervalent Iodine Reagents

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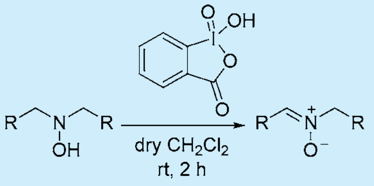
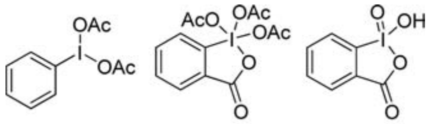
Supporting Information

ABSTRACT: Hypervalent iodine compounds are viable reagents for the oxidation of *N,N*-disubstituted hydroxylamines to the corresponding nitrones, with IBX performing best. The procedure is very simple and user-friendly and affords the target compounds with high efficiency and regioselectivity, highlighting IBX as the reagent of choice for preparation of aldonitrones from nonsymmetric hydroxylamines. Evidence for a mechanism involving nitrogen to iodine coordination has been collected.



13 examples
operationally simple
no chromatography
high yields and regioselectivity

Hypervalent iodine reagents, both of the λ^3 and λ^5 type,[1] have been established as efficient and useful reagents for the oxidation of several organic functional groups. Among the former type, (diacetoxyiodo)benzene (DIB, **1**) is the most popular and employed member, while Dess-Martin periodinane (DMP, **2**) and *o*-iodoxybenzoic acid (IBX, **3**) have been most extensively studied and used as I(V) oxidants (Figure 1).



1, DIB **2**, DMP **3**, IBX

Figure 1. Common commercially available hypervalent iodine oxidizing agents.

For many years, we have been strongly involved in the use of nitrones as useful and versatile synthetic intermediates for the obtainment of alkaloids and other nitrogenated products.[2] Moreover, nitrones are widely used for biological studies as spin trapping reagents and antioxidants in age related diseases.[3] In this context, we have diffusely investigated new simple and practical metal-catalyzed oxidative procedures, with the use of inexpensive oxidants, for the synthesis of nitrones from different nitrogenated precursors,[4] such as secondary amines,[5] imines,[6] and *N,N*-disubstituted hydroxylamines.[7] During these studies, we have observed that common reagents used for the interconversion of alcohols to the corresponding carbonyl derivatives, such as NMO/TPAP, are also able to oxidize *N,N*-disubstituted hydroxylamines to the corresponding nitrones under mild conditions with high chemoselectivity and without formation of byproducts.[8] We therefore envisaged that DMP,[9] one of the currently most used reagents for the mild oxidation of alcohols to aldehydes and ketones,[10] was a suitable candidate to serve our aim in the search for a novel and convenient metal-free synthesis of nitrones.[11] IBX,[12] which is also able to oxidize alcohols and has been used to replace DMP in some applications,[13] was also considered a good candidate. Moreover, IBX has emerged recently as a very versatile oxidant[14] and has been investigated by the Nicolaou group as an oxidant for nitrogenated compounds.[15] Particularly, analogously to the behavior of NMO/TPAP,[16] it was found to oxidize effectively secondary amines to the corresponding imines. Efficient oxidations of *N*-benzylhydroxylamine and *N,O*-dibenzylhydroxylamine to the corresponding oximes were also described;[15] however, no example of *N,N*-disubstituted hydroxylamines as substrates was reported. Finally, DIB was taken into account, as an example of an I(III) oxidant. It was also taken into consideration because of its use as an efficient reagent for the related generation of nitrile oxides from the corresponding oximes, as recently reported by Ciufolini and co-workers.[17,18]

In this Letter we report our results on the oxidation of *N,N*-disubstituted hydroxylamines to the corresponding nitrones by the hypervalent iodine oxidants **1**−**3**, which show IBX as the reagent of choice, with high efficiency and uncommon potentialities for the regioselective oxidation of nonsymmetric hydroxylamines, particularly in the preferential formation of aldo- vs keto-nitrones.

We initially tested the iodine hypervalent oxidants **1**−**3** in the oxidation of simple unfunctionalized and symmetric hydroxylamines **4**−**6** under the same standard reaction conditions in order to compare the efficiency of the three reagents in the desired transformation (Table 1).

The results of oxidation of hydroxylamines **4**−**6** show that all three reagents **1**−**3** perform successfully, affording complete conversions after 2 h in dichloromethane at rt and giving nitrones

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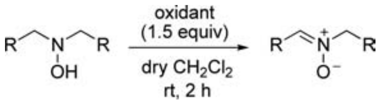
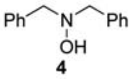
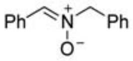
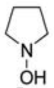
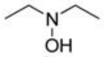
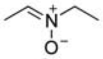
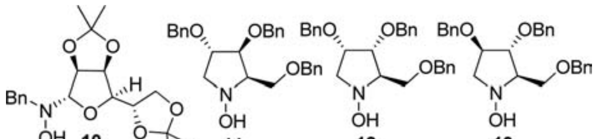
Table 1. Evaluation of Hypervalent Iodine Oxidants 1−3 in the Oxidation of Hydroxylamines to Nitrones[a]

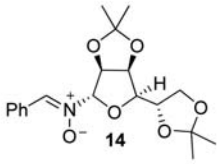
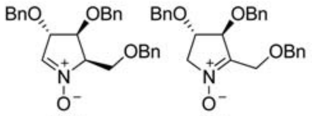
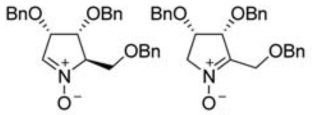
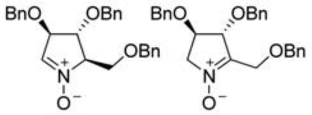


entry	hydroxylamine	nitrone	yield, %[b] DIB	DMP	IBX
1	 4	 7	77	62	95[c]
2	 5	 8	79	75	88
3	 6	 9	67	71	96

[a]Reaction conditions: hydroxylamine (0.25 mmol) in 0.09 M dry CH_2Cl_2, oxidant (1.5 equiv), rt, 2 h. [b]Isolated yield after flash column chromatography, unless otherwise stated. [c]Yield of crude product (>98% purity).

Table 2. Evaluation of Hypervalent Iodine Oxidants 1−3 in the Oxidation of Carbohydrate Derived Hydroxylamines[a]


10 11 12 13

entry	nitrones	yield, % a/b ratio[b] DIB[c]	DMP[c]	IBX
1	 14	63	47	95[d]
2	 15a 15b	39 1:3.3[e]	10 <5:95	100[d] 6:1
3	 16a 16b	40 1.1:1[e]	45 2:1[e]	94[c] >95:5
4	 17a 17b	54 1.1:1	55 1.8:1	89[d] 5:1

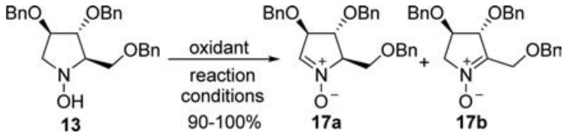
[a]Reaction conditions: hydroxylamine (0.2 mmol) in 0.09 M dry CH_2Cl_2, oxidant (1.5 equiv), rt, 2 h. [b]Determined by integration of ^1H NMR spectrum of the crude reaction mixture, unless otherwise stated. [c]Isolated yield after flash column chromatography, unless otherwise stated. [d]Yield of crude product (>98% purity). [e]Determined on the basis of isolated yield after flash column chromatography.

7−9 in good to excellent yields. IBX stems as the best oxidant; besides the higher yields, a greater advantage is represented by the much easier workup. For example, nitrone **7** was obtained spectroscopically pure in 95% yield by a simple extraction and no further separation was required. Use of a lower amount of IBX was less efficient: oxidation of hydroxylamine **4** required 6 h to go to completion with 1.1 of equiv IBX (91% yield) and afforded only 75% conversion after 24 h with 0.6 equiv of IBX. Notwithstanding IBX appearing optimal, use of DIB as the oxidant is also worth considering due to its lower cost.

In order to check the behavior of the three iodine hypervalent reagents toward structurally more complex substrates, we extended our study to carbohydrate derived hydroxylamines **10−13**, which contain different hydroxyl protecting groups, such as acetonide and benzyl, and are unsymmetric. Consequently, two regioisomeric nitrones, an aldonitrone **a** and a ketonitrone **b**, may originate by dehydrogenation of the less substituted or the more substituted *α* carbon atom, respectively. The issue of regioselectivity in the oxidation of unsymmetric hydroxylamines is still an unmet goal, apart from a few peculiar substrates. The results of oxidation of hydroxylamines **10**, **11**, **12**, and **13** under the same standard conditions are reported in Table 2 in entries 1, 2, 3, and 4, respectively.

These results clearly establish IBX as a superior oxidant for the studied transformation, affording nearly quantitative yields of nitrones also from more challenging functionalized hydroxylamines **10−13** with no loss of stereochemical integrity. Conversely, DMP and DIB performed poorly with these substrates, showing complete conversion but scarce chemoselectivity. Moreover, IBX furnished aldonitrones as major products with considerable regioselectivity, ranging from moderate for hydroxylamines **11** and **13** (Table 2, entries 2 and 4) to complete for **10** and **12** (Table 2, entries 1 and 3). While the complete regioselectivity for **10** was expected since it was also observed with MnO_2,[19] high regioselectivity for hydroxylamines **11−13** has no precedent in related cases. In this respect, the behavior of IBX appears unique, since the other hypervalent iodine reagents display poor, if any, regioselectivity. In order to compare the regioselectivity shown by IBX with that of other typical oxidants for hydroxylamines, compound **13** was oxidized with a variety of reagents (Table 3). All the tested reagents afforded nearly quantitative yields of the two nitrones **17a,b**, but their ratio varied considerably, as well as the time

Table 3. Evaluation of the Aldonitrone/Ketonitrone Regioselectivity in the Oxidation of Hydroxylamine 13 with Several Reagents



entry	oxidant	reaction conditions	17a/17b ratio[a]
1	HgO	CH_2Cl_2, rt, 74 h	1:1
2	DDQ	CH_2Cl_2, rt, 2 min	1:1
3	TPAP/NMO	CH_3CN, rt, 20 h	1:2
4	5% NaClO, aq. 0.5 M $KHSO_4$	CH_2Cl_2, rt, 7 d	5.9:1
5	IBX	CH_2Cl_2, rt, 2 h	5:1

[a]Determined by integration of ^1H NMR spectrum of the crude reaction mixture.

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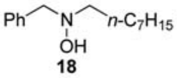
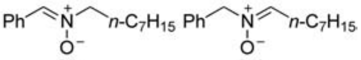
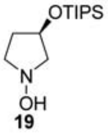
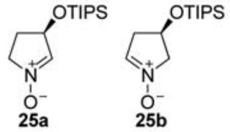
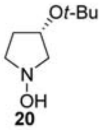
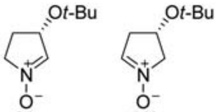
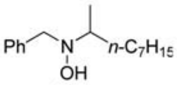
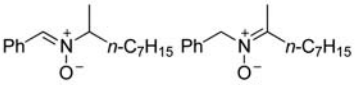
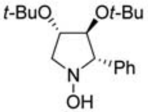
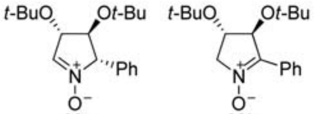
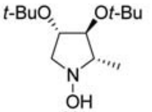
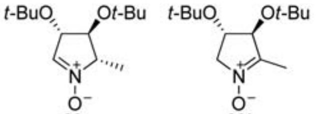
required for completion of the reaction. While HgO and DDQ gave approximately an equimolar amount of the two regioisomeric nitrones (Table 3, entries 1 and 2), TPAP/NMO[8] favored formation of the ketonitrone **17b** (entry 3). Considerable regioselectivity in favor of the aldonitrone **17a** (entry 4) was obtained by the use of bleach in acidic media (pH ≈ 2.8), conditions which were found to speed up the oxidation and slightly favor formation of aldo- vs ketonitrones.[11a] However, this oxidation required long reaction times and gave erratic results, showing low reproducibility. A similar rewarding 5:1 selectivity was obtained with the very reliable and simple oxidation with IBX (entry 5).

The above results demonstrate that IBX is the reagent of choice for the oxidation of hydroxylamines to nitrones among the common hypervalent iodine oxidants, and suggest it may possess unique and superior properties for attaining high regioisomeric ratios from unsymmetric hydroxylamines. In this respect, we checked further the chemo- and regioselectivity of the oxidation with IBX with other unsymmetric hydroxylamines **18−23**, either cyclic or acyclic (Table 4), and possessing the same (entries 1−3) or different (entries 4−6) degree of substitution at the two carbon atoms adjacent to nitrogen. The hydroxylamine **18** afforded quantitatively an equimolar mixture of the two regioisomeric nitrones **24** (entry 1), suggesting that thermodynamic stability of the products does not play a significant role. The two protected 1-hydroxypyrrolidin-3-ols **19** and **20** gave the nitrones **25a** and **26a**, respectively, in significant excess with respect to their regioisomers **25b** and **26b**, as expected on the basis of stereoelectronic considerations and in agreement with results of the oxidation of the same substrates with metal oxides.[22] However, the ratios observed in oxidations with IBX were lower than those obtained with HgO or MnO_2.[22] Then, use of IBX does not give advantages in terms of regioselectivity for the oxidation of unsymmetric hydroxylamines possessing two methylene groups adjacent to nitrogen. Conversely, hydroxylamines **22−23**, possessing a methylene and a methine group at the α and α' positions to nitrogen, showed a great and synthetically significant increase in the nitrone regioisomeric composition in favor of the aldonitrones **28a** and **29a**, when the oxidation was carried out with IBX instead of with MnO_2 (entries 5−6). Particularly remarkable was the oxidation of the acyclic hydroxylamine **21**, which yielded the aldonitrone **27a** almost exclusively (entry 4). Ketonitrones are expected to be favored on thermodynamic grounds, while aldonitrones should be favored sterically (and statistically). Consequently, we may infer that regioselectivity in the oxidation of hydroxylamines with IBX is mostly driven by steric effects.

The mildness and rapidity of this reaction led us to anticipate a chemoselectivity for the oxidation of hydroxylamines compared to other functional groups susceptible to oxidation by IBX. This assumption was confirmed by the completely selective oxidation of hydroxylamine **6** in the presence of 1-hexanol (see Supporting Information).

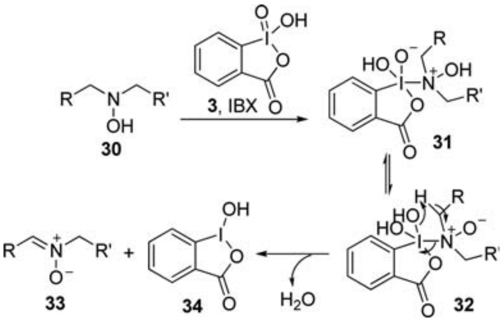
Concerning the mechanism of the oxidation of hydroxylamines with IBX, we propose coordination of the IBX iodine atom at nitrogen, rather than at oxygen, to give adducts **31** (Scheme 1). Spectroscopic evidence substantiating this hypothesis was collected. Indeed, ^1H NMR of the oxidation mixture of hydroxylamine **6** recorded at an early stage showed the splitting of the quartet of the methylene H's α to nitrogen into two multiplets, in agreement with transformation of two equivalent H atoms (A_2X_3 system) into two diastereotopic ones (ABX_3 system) consequent to quaternization of nitrogen (see Supporting Information). Then, the initial stage is similar to that proposed by Nicolaou and co-workers for the IBX oxidation

Table 4. Oxidation of Unsymmetric Acyclic and Cyclic Hydroxylamines with IBX[a]

entry	hydroxylamine	nitrones yield, %[b], **a**/**b** ratio[c]
1	 **18**	 **24a** **24b** 100, 1:1.1
2	 **19**	 **25a** **25b** 92, 3.7:1 (11:1)[20]
3	 **20**	 **26a** **26b** 38, 6:1 (7:1)[7d]
4	 **21**	 **27a** **27b** 73, 70:1
5	 **22**	 **28a** **28b** 89, 4:1 (1.5:1)[21]
6	 **23**	 **29a** **29b** 100, 4.3:1 (2.3:1)[21]

[a] Reaction conditions: hydroxylamine (0.1−1.6 mmol) in 0.09 M dry CH_2Cl_2, IBX (1.5 equiv), rt, 2 h. [b] Yield of crude product (>98% purity). [c] Determined by integration of ^1H NMR spectrum of the crude reaction mixture; in parentheses the ratios obtained by oxidation with HgO (entry 2) or MnO_2 (entries 3, 5, 6).

Scheme 1. Mechanism Proposed for the IBX Oxidation of Hydroxylamines



of amines, and to the best of our knowledge, this finding is the first bit of experimental supporting evidence.[15b] According to their proposal, an ionic mechanism would afford the final nitrones and reduced iodosobenzoic acid **34**. For unsymmetric substrates, bulkiness of the reagent reasonably explains the preferential abstraction of hydrogen from the less substituted carbon atom α to nitrogen, thus accounting for the observed regioselectivity in favor of aldonitrones.

In summary, we have established that hypervalent iodine compounds are viable reagents for the oxidation of *N*,*N*-disubstituted hydroxylamines with IBX being the reagent of choice, affording the corresponding nitrones with high efficiency and unique potentialities for the regioselective oxidation of nonsymmetric hydroxylamines, particularly in the preferential formation of aldo- vs keto-nitrones, for which a 2- to 5-fold increase in regioisomeric ratio was shown in comparison to the most common oxidants for this transformation. Our results highlight the additional use and reactivity of this versatile reagent and disclose a further method for the studied oxidation that is particularly mild and simple to perform, which avoids the use of toxic transition metals and any separation technique in most cases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02029.

Detailed experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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