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Oxidation of Oximes to Nitrile Oxides with Hypervalent Iodine Reagents

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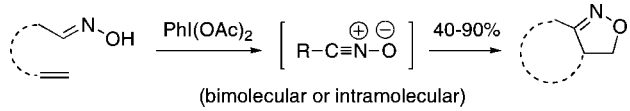
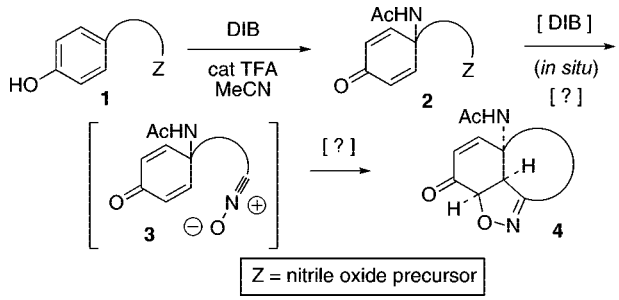
ABSTRACT



Iodobenzene diacetate in MeOH containing a catalytic amount of TFA efficiently oxidizes aldoximes to nitrile oxides. The latter may be trapped in situ with olefins in a bimolecular or an intramolecular mode. The new method enables the execution of tandem oxidative dearomatization of phenols/intramolecular nitrile oxide cycloaddition sequences leading to useful synthetic intermediates.

Hypervalent iodine reagents[1] such as $PhI(OAc)_2$ ("DIB") and $PhI(OCOCF_3)_2$ ("PIFA") react with 4-substituted phenols **1** in the presence of MeCN to furnish compounds **2** (Scheme 1),

Scheme 1. Hypothetical Tandem Oxidative Amidation−Intramolecular Nitrile Oxide Cycloaddition



which are useful building blocks for the synthesis of nitrogenous substances.[2] This is an example of oxidative amidation of phenols.[3] Ongoing work unveiled the desirability of executing the oxidative amidation of a phenol in tandem with an intramolecular nitrile oxide cycloaddition (INOC),[4] leading to tricyclic intermediates **4**. That dienones arising through oxidative dearomatization of phenols are capable of participating in tandem reactions, especially 1,4-addition processes, leading to densely functionalized, synthetically valuable, intermediates is well established. For instance, a tandem oxidative hydroxylation/Michael cyclization[5] of tyrosine derivatives has been used as a key step in the synthesis of *Stemona* alkaloids[6] and of hydroxylated aminoacids related to parkacine, aeruginosine, and castanospermine,[7] while an oxidative amidation/conjugate addition sequence was central to a synthesis of cylindricine C.[8]

(1) Reviews: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Kita, Y. *Yakugaku Zasshi* **2002**, *122*, 1011. (e) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. Monograph: (f) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997.

(2) (a) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175.

(3) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M; Chang, J; Chai, D. *Synthesis* **2007**, 3759.

(4) Reviews: (a) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, 1990; Vol. I, p 77. (b) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. See especially pp 12255−12259.

(5) Reviews: (a) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469. (b) Rodríguez, S.; Wipf, P. *Synthesis* **2004**, 2767.

(6) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225, and references cited therein.

(7) Pierce, J. G; Dhanalakshmi, K.; Fushimi, M.; Cuzzuppe, A.; Wipf, P. *J. Org. Chem.* **2008**, *73*, 7807.

(8) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336.

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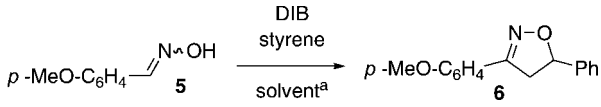
However, the precise transformation depicted in Scheme 1 appears to be undocumented.

An especially direct approach to **4** would materialize if group Z in **1** could be oxidatively converted into a nitrile oxide with the same hypervalent iodine reagent utilized in the oxidative amidation step, but at a slower rate relative to the oxidative amidation reaction proper. This rate difference is essential to ensure efficient intramolecular capture of the nascent nitrile oxide. An attractive solution envisioned that Z should be an aldoxime group. Aldoximes are established precursors of nitrile oxides;[4] moreover, their conversion thereto with PhI=O in $CHCl_3$ is documented.[9] However, such conditions would not permit the occurrence of a simultaneous oxidative amidation step, which requires DIB in fluoro alcohol solvents[3,10] or in MeCN containing a catalytic amount of TFA.[2a] Thus, an initial phase of this work aimed to establish whether aldoximes may be converted into nitrile oxides under conditions that would also promote the oxidative amidation of phenols.

The feasibility of such a transformation was uncertain, because hypervalent iodine reagents could induce oxidative deoximation of the substrates,[11] thereby suppressing nitrile oxide formation. Fortunately, such concerns proved to be unfounded. As shown in Table 1 for the test oxidation of **5**

Table 1. Solvent Effect in the DIB Oxidation of Aldoximes to Nitrile Oxides



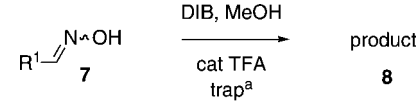
entry	DIB (equiv)	styrene (equiv)	solvent	time (min)	yield[b]
a	1.1	4.0	$CHCl_3$	35	31
b	1.1	1.1	THF	90	28
c	1.1	1.1	THF	240	23
d	1.2	1.4	TFE	15	68
e	1.3	1.3	HFIP	35	54
f	1.3	1.1	HFIP	150	54
g	1.2	4.0	HFIP	45	51
h	1.2	2.0	HFIP	17	64
i	1.2	1.3	MeOH	20	59
j	1.1	1.1	MeCN	60	32
k	1.1	1.1	MeOH+TFA (15 μL)[c]	60	91
l	1.1	1.1	MeCN+TFA (1.2 equiv)[c]	30	51

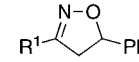
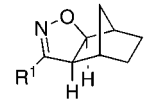
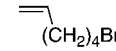
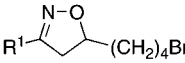
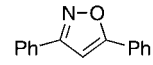
[a] Typical procedure: a solution of oxime (1.5 mmol) in an appropriate solvent (3 mL) was added slowly at rt to a stirred solution of DIB and styrene in the same solvent (3 mL). After the stated time, the mixture was evaporated in vacuo and the residue was purified by flash chromatography (step gradient 5−10% to 15−20% EtOAc/hexanes). [b] After column chromatography. [c] Reactions run with 0.5 mmol of oxime dissolved in 1 mL of solvent and added slowly at rt to a stirred solution of DIB, styrene, and TFA (15 μL) in the same solvent (1 mL).

with DIB in the presence of styrene, fluoroalcohols such as trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) were superior to $CHCl_3$. An excess of DIB or of trap had an insignificant effect on yields. An important finding is that MeOH is nearly as good a solvent as the more costly fluoro alcohols. Furthermore, the yields of reactions run in MeOH improve appreciably upon addition of a small catalytic quantity of TFA, typically 15 μL for a reaction run with about 0.5 mmol of substrate (cf. entry **k**). However, larger amounts of TFA should be avoided (entry **l**). Best results were obtained when the oxime was added to a solution of 1.1 equiv of DIB and 1.1 equiv of olefin at rt.

Table 2 provides representative examples of nitrile oxide generation/trapping in MeOH/cat. TFA in the bimolecular

Table 2. DIB Oxidation of Aldoximes to Nitrile Oxides in MeOH Containing Catalytic TFA



entry	trap	R^1	product	yield[b]
a		Ph		71
b		*m*-O_2N-C_6H_4		91
c		*n*-C_5H_{11}		74
d		$Ph(CH_2)_2$		63
e		Ph		95
f		*m*-O_2N-C_6H_4		77
g		*n*-C_5H_{11}		91
h		$Ph(CH_2)_2$		79
i		*tert*-Bu		75
j		*p*-MeO-C_6H_4		90
k		Ph		83
l		Ph[c]		50

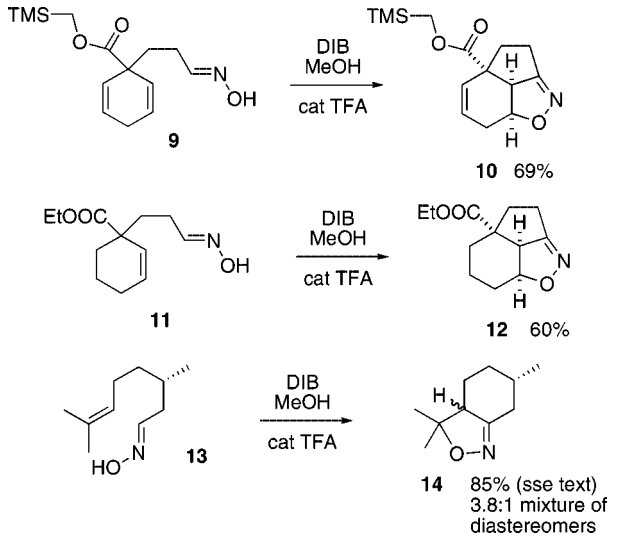
[a] Representative procedure: a solution of oxime (1 mmol) in MeOH (1 mL) was added slowly (syringe pump, 1 h) at rt to a stirred solution of DIB (1.1 equiv) and an olefin (1.1 equiv) in MeOH (2 mL) containing TFA (15 μL). A white precipitate formed immediately and then slowly dissolved as the reaction progressed. Upon consumption of the oxime (TLC, ca. 1 h), the mixture was concentrated in vacuo and the residue was purified by flash chromatography (step gradient 5−10% to 20% EtOAc/hexanes in each case). [b] After column chromatography. [c] Variable quantities of 3,5-diphenyl-1,2,4-oxadiazole 4-oxide (dimer of benzonitrile oxide) were recovered from this reaction.

regime. Yields of chromatographically purified isoxazoline are uniformly good to excellent. Replacing the olefinic trap with a terminal alkyne resulted in formation of a fully aromatic isoxazole, but in lower yields and with variable

efficiency. It seems likely that this was due to a competing in situ formation of alkynyliodonium species[12] and ensuing degradation thereof in the presence of nucleophilic MeOH. Thus, DIB oxidation of benzaldoxime in the presence of phenylacetylene furnished 3,5-diphenylisoxazole in 50% yield (Table 2, entry I), together with a significant amount of benzonitrile oxide dimer (3,5-diphenyl-1,2,4-oxadiazole-4-oxide). By contrast, an analogous reaction with 1-hexyne as the trap provided the isoxazole in only 16% yield.

Intramolecular variants of the reaction were examined using substrates **9**,[13] **11**,[14] and **13**, which cyclized in 60−70% yield under the influence of DIB in MeOH/cat. TFA (Scheme 2).[15] Citronellal-derived isoxazoline **14** was obtained as mixture of two diastereomers in a 3.8:1 ratio.

Scheme 2. Intramolecular Variants of the Reaction

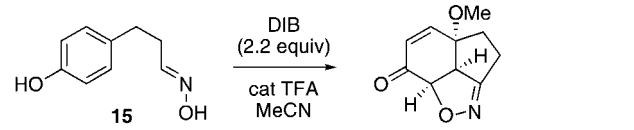


This material appeared to be volatile, and it was lost during vacuum concentration of chromatographic fractions. Accordingly, the reaction yield was calculated to be 85% by integration of an NMR spectrum obtained from a solution of crude **14** containing a known amount of 1,3,5-trimethoxybenzene as an internal standard. Only a portion of crude material was purified for the purpose of characterization. A pure sample of the major isomer thus obtained had $[\alpha]^{20}_{D} = -87.0$ (CH_2Cl_2, $c = 0.01$). However, the configuration of this substance remains undetermined.[16]

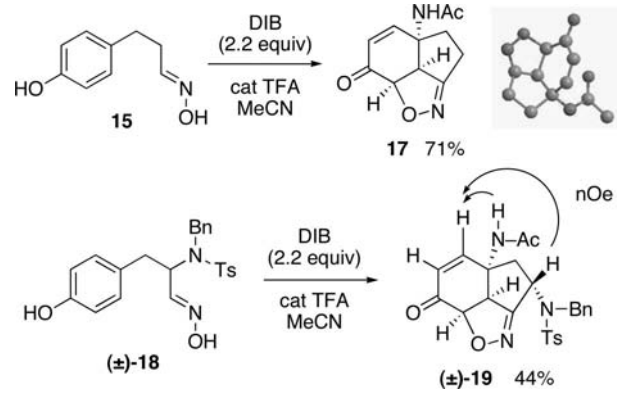
The foregoing experiments indicated that the rate of DIB oxidation of aldoximes to nitrile oxides (45−60 min for complete conversion) was significantly slower than that of oxidative dearomatization of a typical phenol (a virtually instantaneous reaction). This boded well for the feasibility of the sequence depicted in Scheme 1.

Oxime **15** (Scheme 3) served to explore the tandem oxidative methoxylation of the phenol/INOC reaction. Pleasingly, compound **16** was isolated in 51% yield after chromatography upon treatment of **15** with 2.2 equiv of DIB in MeOH/catalytic TFA. The substance was quite polar, and it seemed to adsorb strongly onto silica gel, causing substantial losses upon chromatography. The NMR yield of **16**, recorded as detailed above for **14** (1,3,5,-trimethoxybenzene as the internal standard), was 65%. With these encouraging results in hand, we turned our attention to the chemistry of Scheme 4. Reaction of **15** with DIB in MeCN in the presence of TFA afforded **17** in 71% yield after chromatography. The structure of this product was ascertained by X-ray diffractometry.[17] It is recognized that the INOC step induces

Scheme 3. Tandem Oxidative Methoxylation−INOC



Scheme 4. Tandem Oxidative Amidation−INOC



(9) Tanaka, S.; Ito, M.; Kishikawa, K.; Kohmoto, S.; Yamamoto, M. *Nippon Kagaku Kaishi* **2002**, *3*, 471.

(10) Fluoroalcohol solvents are particularly efficacious in DIB-mediated oxidations: Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857. See also refs 1d and 3.

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(13) Prepared from 1-[2-(1,3-dioxolan-2-yl)ethyl]- 2,5-cyclohexadiene-1-carboxylic acid [(a) Chuang, C. P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3218. (b) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* 1986, *108*, 5893]starting with reaction with $TMSCH{=}N_2$. Interestingly, the TMS group remained in place throughout the sequence. For details, see the Supporting Information.

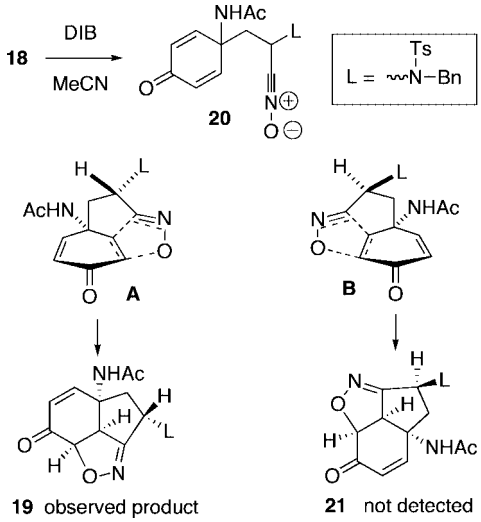
(14) Prepared from ethyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-2-oxocyclohexanecarboxylate (Singh, K. P.; Mandell, L. *Chem. Ber.* **1963**, *96*, 2485.) as described in the Supporting Information.

(15) The oxidative cyclization of **9** was more efficient when run in the significantly costlier HFIP as the solvent (85% chromatographed yield). Details are provided as Supporting Information.

desymmetrization of the dienone; in particular, it causes the NHAc-bearing carbon to become stereogenic. The configuration of this emerging stereocenter could be controlled if the intermediate nitrile oxide were to add selectively to one of the two enantiotopic π bonds of the dienone. Such a theme is apparent from this laboratory's past efforts on the total synthesis of FR-901483[18] and cylindricine C.[8]

The search for an artifice that might attain such a goal in the present case led us to oxime (±)-**18** (Scheme 4).[19]

Scheme 5. Presumed Course of the Tandem Oxidative Amidation−INOC of Oxime **18**



Exposure of this material to DIB/TFA in MeCN resulted in formation of (±)-**19** as the sole identifiable product in 44% chromatographed yield. The configuration of **19** was assigned on the basis of the indicated nuclear Overhauser enhancements (NOE; 2D NOESY spectroscopy). The observed stereoselectivity may be rationalized (Scheme 5) by considering that the presumed nitrile oxide **20** arising upon oxidation of **18** can undergo cyclization via transition state **A**, which leads to the observed product **19**, or **B**, which would furnish the diastereomeric product **21**. Transition state **B** appears to be disfavored relative to **A**, because the bulky *N*-benzyl tosylamido group (represented as L in Scheme 5) is oriented inside the concavity of the developing tricyclic system. This engenders an unfavorable steric compression that is absent in **A**, wherein L resides on the convex face of the incipient product. Thus, the reaction forms **19**selectively.

In summary, this work has determined that $PhI(OAc)_2$ is a good oxidant for the conversion of aldoximes into nitrile oxides, and that such a transformation may be carried out in tandem with the oxidative dearomatization (methoxylation or amidation) of a phenol. The value of the resulting intermediates as educts for the synthesis of nitrogenous substances is currently being evaluated and pertinent results will be detailed in due course.

Acknowledgment. We thank the University of British Columbia, the Canada Research Chair Program, NSERC, CIHR, CFI, and MerckFrosst Canada for financial support.

Supporting Information Available: Experimental procedures and characterization data for new compounds, hardcopy NMR (^{1}H and ^{13}C) spectra of several molecules, and details of the X-ray diffractometric study of **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The resonances of the axial proton on the methylene adjacent to the oximino group (ca. 1.8 ppm) and of the methyl-bearing methine (ca. 1.50 ppm) overlap with those of other ring protons, preventing the accurate determination of coupling constants and, hence, of the configuration.

(17) Relevant data are provided as Supporting Information.

(18) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765.

(19) The preparation of **18** is detailed in the Supporting Information.