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Generation of Nitrile Oxides from Oximes Using *t*-BuOI and Their Cycloaddition

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ABSTRACT

***tert*-Butyl hypoiodite (*t*-BuOI) was found to be a powerful reagent for the cycloaddition of oximes and alkenes/alkynes, leading to the formation of a variety of isoxazolines or isoxazoles under mild conditions.**

The 1,3-dipolar cycloaddition of nitrile oxides to C−C unsaturated bonds has proven to be very useful for the synthesis of isoxazolines and isoxazoles.[1] These frameworks are found in a wide variety of nitrogen heterocycles that are molecular components of a large number of natural products and biologically active compounds.[2] Isoxazoline adducts that are produced in nitrile oxide/alkene cycloaddition reactions can be used as masked *β*-hydroxy carbonyl aldolate[3] and *β*-amino alcohol[4] equivalents. Nitrile oxides are commonly generated by the elimination of HCl from hydroximinoyl chlorides in the presence of a base.[5] Hydroximinoyl chlorides can be prepared from the corresponding oximes, derived from aldehydes, and electrophilic chlorine-containing sources, such as *N*-chlorosuccinimide (NCS), NaOCl, Cl_2, etc.[6] Although there are a few reports on the use of an electrophilic bromine reagent, specifically *N*-bromosuccinimide (NBS), for generating nitrile oxides from oximes,[7] the use of an electrophilic iodine reagent has not been reported to date. As an alternate approach, dehydrative[8] and oxidative[9] processes were developed, and these methods have been applied to the synthesis of complex molecules. In our continuing interest in the area of monovalent iodine-containing compounds, *tert*-butyl hypoiodite (*t*-BuOI) was

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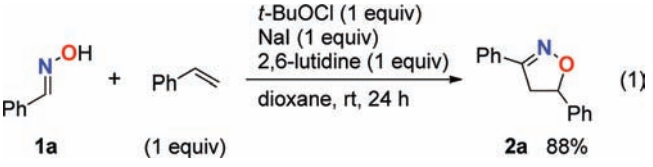
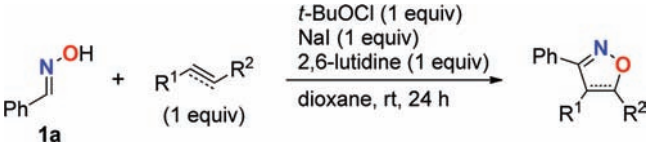
found to be a versatile reagent for the synthesis of nitrogen-containing heterocycles from simple amides and alkenes[10] and for CO_2 fixation by allyl alcohols.[11] From these points of view, herein we report an in situ generation method for nitrile oxides from oximes using *t*-BuOI.

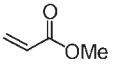
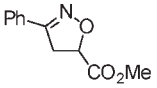
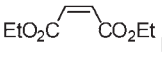
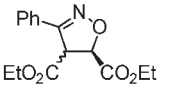
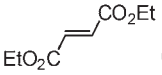
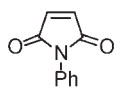
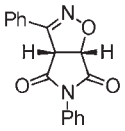
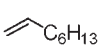
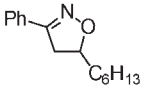
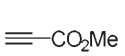
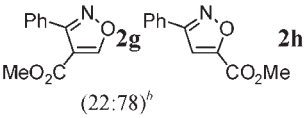
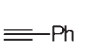
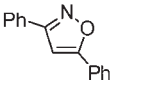
The reagent *t*-BuOI can be readily prepared in situ from commercially available *tert*-butyl hypochlorite (*t*-BuOCl) and sodium iodide (NaI).[12] Initially, we examined a cycloaddition reaction involving benzaldoxime and styrene in the presence of an equimolar amount of *t*-BuOI. When benzaldoxime (**1a**) and styrene were treated with *t*-BuOI (1 equiv) in acetonitrile at room temperature for 24 h, isoxazoline **2a** was produced in 45% yield. To improve the efficiency of the reaction, a variety of solvents and temperatures were screened. When dioxane was used as a solvent, the desired isoxazoline was produced in 54% yield. Since HI is liberated during the reaction, bases were added to the system. As a result of the screening of bases, 2,6-lutidine was found to be a suitable base for the cycloaddition to afford **2a** in 88% yield (eq 1). To confirm the superiority of the system, *t*-BuOCl and *N*-iodosuccinimide (NIS) were employed separately to the reaction, in the presence of 2,6-lutidine, and both reagents failed to provide the desired product **2a** in sufficient chemical yield (with *t*-BuOCl: 44% yield; with NIS: 25% yield).



Having optimized the reaction conditions and reagents, we explored the scope of the reaction with respect to substrates (dipolarophiles, Table 1). A terminal electron-deficient olefin was transformed into the corresponding isoxazoline **2b** in excellent yield with complete regioselectivity (entry 1). When geometric isomers (ethyl maleate and fumarate) were used, diastereomers **2c** and **2d** were obtained in both cases (entries 2 and 3). The stereochemistry of the major adducts was reflected by the geometry of the dipolarophiles. In order to clarify the origin of the production of the minor adducts, each single stereoisomer **2c** or **2d** was treated separately with 2,6-lutidine, and partial *cis*−*trans* isomerization of the stereoisomers was observed in both cases. This result indicates that the reaction proceeds in a concerted manner and that the resulting adducts were successively isomerized by the base. *N*-Phenylmaleimide functioned as a dipolarophile to afford the adduct in good yield (entry 4). An aliphatic terminal olefin, 1-octene, was applicable to the reaction, with the regioselective formation of the adduct (entry 5). Although the reaction of aldoxime **1a** with methyl propiolate gave a mixture of regioisomers, the reaction with phenylacetylene yielded a sole regioisomer (entries 6 and 7).

Table 1. Cycloaddition of Benzaldoxime Using *t*-BuOI[a]



entry	dipolarophile	product(s)		yield (%)
1			**2b**	98
2		 (*cis*:*trans* = 89:11)[b]	**2c, d**	72
3		**2c, d** (*cis*:*trans* = 8:92)[b]		71
4			**2e**	92
5			**2f**	70
6		 (22:78)[b]	**2h**	71
7			**2i**	75

[a] Reaction conditions: benzaldoxime (0.25 mmol), dipolarophile (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol), 2,6-lutidine (0.25 mmol), dioxane (5 mL). [b] Determined by ^{1}H NMR.

As shown in Table 2, the reaction tolerates a wide diversity of substituents at the para position of benzaldoxime. Benzaldoximes containing both electron-donating and -withdrawing groups reacted readily with styrene, selectively leading to the corresponding isoxazolines in good yields.

The scope of the reaction was also extended to various aldoximes (Table 3). Aldoximes substituted with alkyl groups derived from acetaldehyde, butanal, and cyclohexyl carbaldehyde were converted into the corresponding

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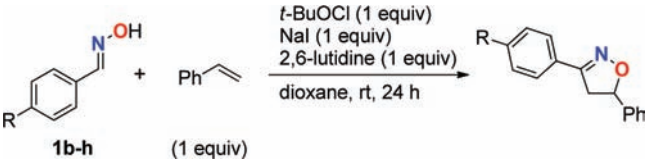
Table 2. Cycloaddition of *p*-Substituted Benzaldoximes Using *t*-BuOI[a]

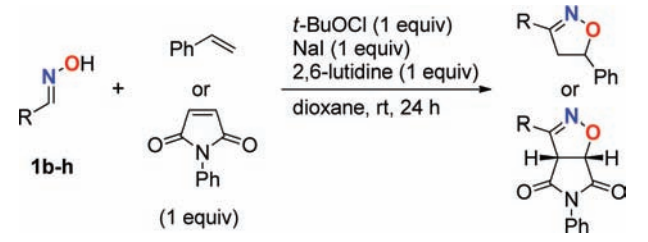


entry	R	yield (%)
1	OMe (**1b**)	71 (**2j**)
2	Me (**1c**)	76 (**2k**)
3	NO_2 (**1d**)	83 (**2l**)
4	CF_3 (**1e**)	98 (**2m**)
5	CN (**1f**)	84 (**2n**)
6	Br (**1g**)	84 (**2o**)
7	Cl (**1h**)	86 (**2p**)

[a] Reaction conditions: aldoxime (0.25 mmol), styrene (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol), 2,6-lutidine (0.25 mmol), dioxane (5 mL).

nitrile oxides, followed by cycloaddition with styrene or *N*-phenylmaleimide, giving a variety of isoxazoline derivatives **2q**−**v** in moderate to good yields (entries 1−6). The reactions of aldoximes derived from alkanals having a phenyl group with *N*-phenylmaleimide proceeded with good yields (entries 7 and 8).

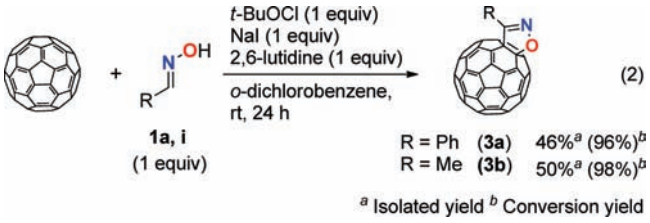
Table 3. Cycloaddition of Aldoximes Using *t*-BuOI[a]



entry	R	dipolarophile	yield (%)
1	Me (**1i**)	styrene	65 (**2q**)
2	*n*-Pr (**1j**)	styrene	67 (**2r**)
3	Me (**1i**)	*N*-phenylmaleimide	82 (**2s**)
4	*n*-Pr (**1j**)	*N*-phenylmaleimide	85 (**2t**)
5	*c*-hex (**1k**)	styrene	81 (**2u**)
6	*c*-hex (**1k**)	*N*-phenylmaleimide	92 (**2v**)
7	$PhCH_2$ (**1l**)	*N*-phenylmaleimide	80 (**2w**)
8	$PhCH_2CH_2$ (**1m**)	*N*-phenylmaleimide	80 (**2x**)

[a] Reaction conditions: aldoxime (0.25 mmol), dipolarophile (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol), 2,6-lutidine (0.25 mmol), dioxane (5 mL).

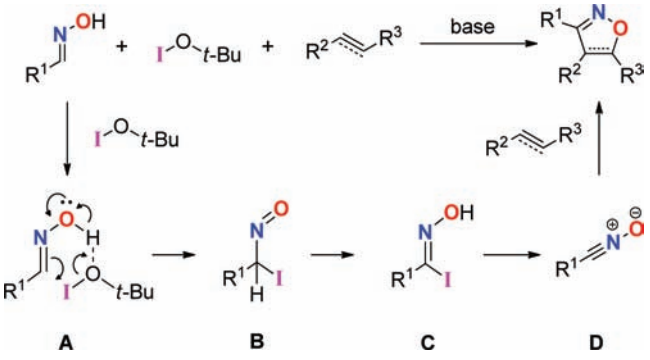
The present cycloaddition was also found to be applicable to C_{60} (eq 2). When C_{60} was treated with benzaldoxime (**1a**) or acetaldoxime (**1i**) in the presence of *t*-BuOCl, NaI, and 2,6-lutidine in *o*-dichlorobenzene, which is a commonly used solvent for dissolving C_{60}, at room temperature for 30 min, isoxazoline-fused C_{60} derivatives **3a** and **3b** were obtained in good isolation yield along with excellent conversion yield.[13]



(2)

Although the precise reaction mechanism is unclear at present, the proposed mechanism shown in Scheme 1 is supported by the experimental findings. Since it is known that *t*-BuOCl reacts rapidly with NaI,[10a] the reaction of benzaldoxime and *t*-BuOI was monitored by ^{1}H NMR spectroscopy. When *t*-BuOI was added to a dioxane-d_8 solution of benzaldoxime, the signals corresponding to hydrogens attached to the imine carbon (δ 8.06 ppm) and the oxygen (δ 9.79 ppm) on benzaldoxime disappeared, and a broad singlet at δ 10.8 ppm was observed, which disappeared when one drop of D_2O was added to the solution.[14] These results indicate the formation of an imidoyl iodide intermediate **C** by the reaction of benzaldoxime and *t*-BuOI. Thus, the most likely pathway for the cycloaddition is proposed to be as follows: (1) α-iodonitroso intermediate **B** is generated through iodination and deprotonation of aldoxime with *t*-BuOI; (2) the resulting intermediate **B** smoothly tautomerizes to the oxime derivative **C**, followed by the elimination of HI in the presence of a base to generate the nitrile oxide **D**, which then participates in a cycloaddition to an unsaturated bond, giving an isoxazoline or isoxazole.

Scheme 1. Plausible Reaction Pathway



In summary, an efficient, simple, and general method for the synthesis of a variety of isoxazolines and isoxazoles by the reaction of oximes and alkenes/alkynes in the presence of *t*-BuOI and a base is described. This is

(13) When dioxane was used as a solvent, the reaction did not proceed at all, probably due to the extremely poor solubility of C_{60} in dioxane.

(14) See the Supporting Information.

the first report of a method for the generation of nitrile oxides using an electrophilic iodine compound, and *t*-BuOI is a versatile reagent for the synthesis of heterocyclic compounds. The application of the potential reagent, *t*-BuOI, to other organic reactions is currently in progress.

Supporting Information Available. General procedures, spectral data for compounds, verification experiment for isomerization of isoxazolines **2c** and **2d** in the presence of 2,6-lutidine, and monitoring of the reaction of benzaldoxime and *t*-BuOI by ^{1}H NMR. This material is available free of charge via the Internet at http://pubs.acs.org.