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Radical oxyamination of vinyl azides with *N*-hydroxyphthalimide under the action of [bis(trifluoroacetoxy)iodo]benzene

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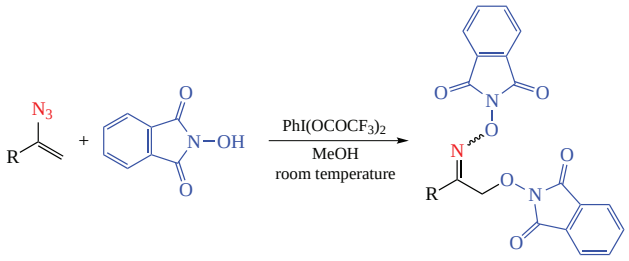
***O,O'*-Bis(phthalimido)-modified 2-(hydroxyimino)ethanols containing N–O–N fragment were synthesized in high yields *via* the reaction of vinyl azides with *N*-hydroxyphthalimide under the action of hypervalent iodine-based oxidant. The reaction proceeds under mild conditions and is compatible with a wide range of vinyl azides. Presumably, the process starts with the oxidative formation of phthalimide-*N*-oxyl radical, followed by its addition to vinyl azide with the subsequent trapping of the generated iminyl radical with the second phthalimide-*N*-oxyl radical.**

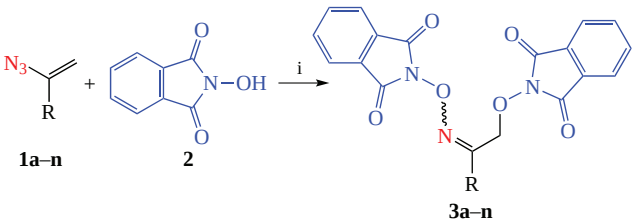


14 examples, up to 79% yield

Keywords: free radicals, imides, *N*-oxyl radicals, *N*-hydroxyphthalimide, vinyl azides, hypervalent iodine.

In recent years, the selective functionalization of double bonds has been studied quite intensively as a versatile method for the synthesis of complex molecules in a minimum number of steps.[1] Approaches involving free radical reactions are of particular interest due to their unusual mechanisms.[2] As a result, unexpected and valuable products can be obtained, which are sometimes unavailable through other synthetic routes.[3] Vinyl azides which contain azido group and other geminal substituent[4] possess interesting reactivity in radical reactions, namely, addition of radical species to the C=C bond results in elimination of molecular nitrogen and generation of iminyl radicals.[5]

Here, we report on the hypervalent iodine-mediated reaction between vinyl azides **1a–n** and *N*-hydroxyphthalimide (NHPI) **2** (Scheme 1). Previously, we found that electric current and cerium(IV) ammonium nitrate, $(NH_4)_2Ce(NO_3)_6$, are able to mediate this process.[6] The hypervalent iodine-based reagents seriously differ from other oxidants in terms of reaction mechanisms and intermediates. In this work, we disclosed that oxidative generation of phthalimide-*N*-oxyl (PINO) radical under the action of hypervalent iodine-based compounds triggered a chain of free-radical transformations resulting in *O,O'*-bis(phthalimido)-modified 2-(hydroxyimino)ethanols bearing a quite rare N–O–N fragment.



1a–n **2** **3a–n**

a	R = Ph, 70%	**h**	R = 2-FC_6H_4, 68%
b	R = 4-MeC_6H_4, 52%	**i**	R = 3-ClC_6H_4, 79%
c	R = 3-MeC_6H_4, 69%	**j**	R = 2-ClC_6H_4, 67%
d	R = 4-$Bu^tC_6H_4$, 51%	**k**	R = 4-BrC_6H_4, 72%
e	R = 4-$MeOC_6H_4$, 40%	**l**	R = 3-BrC_6H_4, 62%
f	R = 4-$AcOC_6H_4$, 68%	**m**	R = 1-benzimidazolyl, 50%
g	R = 4-FC_6H_4, 79%	**n**	R = CO_2Me, 51%

Scheme 1 *Reagents and conditions*: **1a–n**/**2** molar ratio 1 : 2, $PhI(OCOCF_3)_2$ (1.2 equiv.), MeOH, 20–25 °C, 20 min (for more details, see Online Supplementary Materials).

Initially, we studied the model reaction of α-phenylvinyl azide **1a** with NHPI **2** under the action of hypervalent iodine-based oxidants. The effects of the solvent nature, the amount and type of oxidant and reaction time on yield of *O,O'*-bis(phthalimido)-modified 2-(hydroxyimino)ethanol **3a** are outlined in Table 1. Initial reaction conditions were chosen according to our previous experience on oxidative transformations of other types of unsaturated compounds, styrenes without leaving groups and possibilities of iminyl radicals formation.[7] The reaction between **1a** and **2** in the presence of two-electron oxidant, [bis(acetoxy)iodo]benzene $PhI(OAc)_2$ (0.6 mol per 1 mol of NHPI **2**), in MeOH resulted in a 42% yield of **3a** (entry 1). The influence of the nature of solvent on **3a** yield was evaluated in entries 2–10. Carrying out the reaction in acetone, MeCN, CH_2Cl_2, $Cl(CH_2)_2Cl$, EtOH, PhMe, CF_3CH_2OH, THF and AcOH did not provide better results in comparison with MeOH. Change of hypervalent iodine-based oxidant to [bis(trifluoroacetoxy)iodo]benzene [$PhI(OCOCF_3)_2$] provided **3a** in a 58% yield (entry 11). When the oxidant amount was increased from 0.6 to 1.0 mmol or decreased to 0.5 mmol, yield of **3a** dropped to 50 and 54%, respectively (entries 12 and 13). Screening of the reaction time (entries 14–16) demonstrated that the highest yield of **3a** was achieved when the reaction was performed for 20 min (74%, entry 15).

It is important to note that the discovered reaction does not proceed under the action of traditional initiators such as azobisisobutyronitrile (AIBN) or *m*-chloroperbenzoic acid

Table 1 Optimization of the reaction conditions for the synthesis of *O*,*O*′-bis(phthalimido)-modified 2-(hydroxyimino)ethanol **3a** from α-phenylvinyl azide **1a** and NHPI **2**.[a]

Entry	Oxidant (molar ratio to **2**)	Solvent	Time/min	Yield of **3a** (%)[b]
1	$PhI(OAc)_2$ (0.6)	MeOH	10	42
2	$PhI(OAc)_2$ (0.6)	acetone	10	35
3	$PhI(OAc)_2$ (0.6)	MeCN	10	32
4	$PhI(OAc)_2$ (0.6)	CH_2Cl_2	10	29
5	$PhI(OAc)_2$ (0.6)	$Cl(CH_2)_2Cl$	10	25
6	$PhI(OAc)_2$ (0.6)	EtOH	10	24
7	$PhI(OAc)_2$ (0.6)	PhMe	10	22
8	$PhI(OAc)_2$ (0.6)	CF_3CH_2OH	10	17
9	$PhI(OAc)_2$ (0.6)	THF	10	17
10	$PhI(OAc)_2$ (0.6)	AcOH	10	15
11	$PhI(OCOCF_3)_2$ (0.6)	MeOH	10	58
12	$PhI(OCOCF_3)_2$ (1.0)	MeOH	10	50
13	$PhI(OCOCF_3)_2$ (0.5)	MeOH	10	54
14	$PhI(OCOCF_3)_2$ (0.6)	MeOH	5	53
15	**$PhI(OCOCF_3)_2$ (0.6)**	**MeOH**	**20**	**74 (70, 67[c])**
16	$PhI(OCOCF_3)_2$ (0.6)	MeOH	30	62

[a] Reaction conditions: to a solution of α-phenylvinyl azide **1a** (73 mg, 0.5 mmol) and NHPI **2** (163 mg, 1.0 mmol) in the specified solvent (5 ml), oxidant (0.6–1.0 mmol) was added, and the mixture was stirred at 20–25 °C for 5–30 min. [b] NMR yield; isolated yield is given in parentheses. [c] 10 mmol (1.45 g) of **1a**, 20 mmol of **2** (3.26 g) and 12 mmol (5.16 g) of $PhI(OCOCF_3)_2$ were used; isolated yields are given.

(mCPBA), that indicates the exceptional role of hypervalent iodine-based oxidants in the process under study.

Thus, according to experimental data, optimal conditions for the synthesis of **3a** from α-phenylvinyl azide **1a** and NHPI **2** call for conducting the process applying $PhI(OCOCF_3)_2$ as the oxidant in MeOH for 20 min (see Table 1, entry 15).

With the optimized reaction conditions in hand, a wide range of *O*,*O*′-bis(phthalimido)-modified 2-(hydroxyimino)ethanols **3a**–**n** were synthesized from vinyl azides **1a**–**n** and NHPI **2** (see Scheme 1). Various 1-azidoethylenes **1g**–**l** with electron-withdrawing groups resulted in the corresponding products **3g**–**l** in good yields (62–79%). When α-arylvinyl azides **1b**–**f** containing electron-donating groups were used as the starting reagents, the desired products **3b**–**f** were obtained in slightly lower yields (40–69%). It should be also noted that hetaryl- and alkyl-substituted vinyl azides **1m**,**n** are also compatible with the process. Yields of the corresponding oxyamination products **3m**,**n** were 50 and 51%, respectively. Successful multigram synthesis of product **3a** (10 mmol of vinyl azide **1a** and 20 mmol of NHPI **2**) under the optimized conditions (Table 1, entry 15) showed that this approach could be used as a preparative route to such family of organic compounds.

All products **3a**–**n** were obtained as an inseparable mixture of *E*- and *Z*-isomers with a ratio from 0.12 : 1 to 0.92 : 1. No correlation was revealed between the substituent nature and the ratio of isomers. However, a shift towards excess of one of the isomers was observed depending on a position of the substituent in the aromatic ring of the product molecule: 0.76–0.92 : 1 for 4-substituted (except for 4-Bu^t), 0.78–0.84 : 1 for 3-substituted and 0.39–0.58 : 1 for 2-substituted ones. In the case of products with benzimidazole and ester substituents, a significant excess of one of the isomers was observed (0.16 : 1 and 0.12 : 1, respectively).

As mentioned earlier there are other methods for the synthesis of *O*,*O*′-bis(phthalimido)-modified 2-(hydroxyimino)ethanols from vinyl azides, *viz*. under the action of electric current or in the presence of $(NH_4)_2Ce(NO_3)_6$, providing yields comparable to the present protocol. In both of these methods column chromatography is required to obtain pure desired product. The herein developed method is characterized by higher synthetic utility, since it allows one to obtain the desired product without the use of chromatographic purification. In the course of the reaction, the products precipitate from the reaction mixture; further they are filtered, washed with methanol and dried, which leads to the analytically pure products **3**. Also the reaction in the presence of hypervalent iodine oxidant allows one to avoid usage of heavy-metal compounds and special electrochemical equipment.

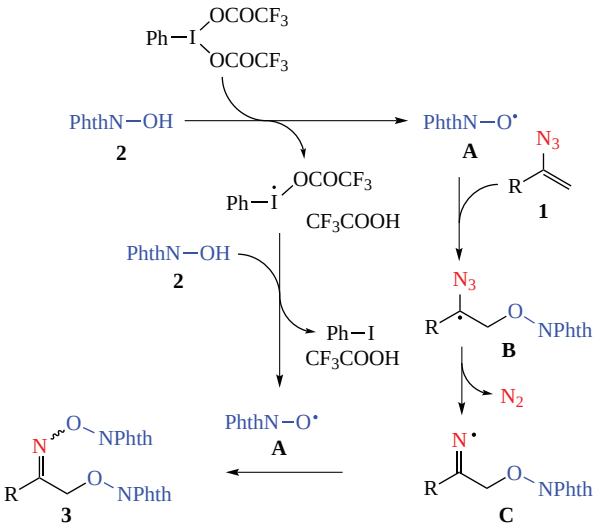


Figure 1 Mechanism for radical oxyamination of vinyl azides **1** with NHPI **2** under the action of hypervalent iodine.

Based on the literature data concerning the generation of PINO radicals from NHPI under the action of hypervalent iodine compounds[7(a)] and the addition of radical species to vinyl azides,[4(c)] we proposed a plausible mechanism for the formation of *O*,*O*′-bis(phthalimido)-modified 2-(hydroxyimino)ethanols **3** from vinyl azides **1** and NHPI **2** under the action of $PhI(OCOCF_3)_2$ (Figure 1).

The reaction begins from the PIFA-mediated formation of two equivalents of PINO radical **A** from NHPI **2**, followed by its addition to the C=C bond of vinyl azide **1**. Nitrogen elimination from the resulting C-centered radical **B** occurs with the formation of iminyl radical **C**. Finally, **C** is intercepted with the second PINO radical **A** to form product **3**.

In summary, the method proposed for the synthesis of *O*,*O*′-bis(phthalimido)-modified 2-(hydroxyimino)ethanols using *N*-hydroxyphthalimide/[bis(trifluoroacetoxy)iodo]benzene system is suitable for the oxyamination of various vinyl azides containing aryl, hetaryl, and alkyl substituents. The main features of this transformation are the development of one step experimental procedure, application of available vinyl azides, NHPI and $PhI(OCOCF_3)_2$, and simplicity of product isolation.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.004.

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